(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 888 349 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
22.05.2002 Bulletin 2002/21

(21) Application number: **97901014.7**

(22) Date of filing: **13.01.1997**

(51) Int Cl.[7]: **C07D 487/04**, A61K 31/505

(86) International application number:
PCT/EP97/00127

(87) International publication number:
WO 97/27199 (31.07.1997 Gazette 1997/33)

(54) PYRROLOPYRIMIDINES AND PROCESSES FOR THEIR PREPARATION

PYRROLOPYRIMIDINEN UND VERFAHREN ZU DEREN HERSTELLUNG

PYRROLOPYRIMIDINES ET LEURS PROCEDES DE PREPARATION

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **23.01.1996 CH 17596**

(43) Date of publication of application:
07.01.1999 Bulletin 1999/01

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  BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
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  Designated Contracting States:
  AT

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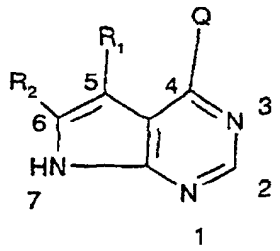
(56) References cited:
EP-A- 0 514 540

EP 0 888 349 B1

Description

[0001] The invention relates to 7H-pyrrolo[2,3-d]pyrimidine derivatives and to processes and novel intermediates for their preparation, to pharmaceutical formulations comprising such derivatives, and to the use of those derivatives as medicaments, and to their use in the preparation of medicaments.

[0002] The compounds according to the invention are compounds of formula I



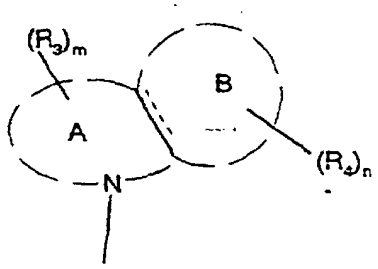
(I)

wherein

R_1 and R_2 are each independently of the other
lower alkyl; monohalo-, dihalo- or trihalo-lower alkyl; lower alkoxy; phenyl that is unsubstituted or substituted by halogen, monohalo-, dihalo- or trihalo-lower alkyl, carbamoylmethoxy, carboxy-methoxy, benzyloxycarbonyl-methoxy, lower alkoxycarbonyl-methoxy, phenyl, amino, amino-lower alkyl, lower alkanoylamino, lower alkoxycarbonylamino, phenyl-lower alkoxycarbonylamino, furoyl, thienylcarbonyl, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, lower alkoxy, lower alkanoyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, N-(N',N'-di-lower alkylaminomethylidene)-amino, N-((N',N'-di-lower alkylamino)-(lower alkyl)-methylidene)-amino, guanidino, ureido, N^3-lower alkylureido, N^3,N^3-di-lower alkylureido, thioureido, N^3-lower alkylthioureido, N^3,N^3-di-lower alkylthioureido, lower alkanesulfonylamino, benzene- or naphthalene-sulfonylamino that is unsubstituted or lower alkyl-substituted at the benzene or naphthalene ring, azido or by nitro; hydrogen; unsubstituted or halo- or lower alkyl-substituted pyridyl; N-benzyl-pyridonium; naphthyl; cyano; carboxy; lower alkoxycarbonyl; carbamoyl; N-lower alkyl-carbamoyl; N,N-di-lower alkyl-carbamoyl; N-benzyl-carbamoyl; formyl; lower alkanoyl; lower alkenyl; lower alkenyloxy; or lower alkyl substituted by halogen, amino, lower alkylamino, piperazino, di-lower alkylamino, phenylamino or phenyl (each unsubstituted or substituted in the phenyl moiety by halogen, lower alkyl, hydroxy, lower alkanoyloxy, lower alkoxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, amino, amino-lower alkyl, lower alkanoylamino, lower alkylamino, N,N-di-lower alkylamino or by trifluoromethyl), hydroxy, lower alkoxy, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, mercapto or by a radical of the formula R_5-S(O_q)- wherein R_5 is lower alkyl and q is 0, 1 or 2, or

R_1 and R_2 together form an alkylene chain having from 2 to 5 carbon atoms which is unsubstituted or substituted by lower alkyl,

Q is heterocyclyl bonded *via* a ring nitrogen atom and having the formula IA



(IA)

wherein

m and n are each independently of the other from 0 to 3,

R_3 and R_4 are each independently of the other selected from lower alkyl; amino-lower alkyl; N-lower alkyl-amino-lower alkyl; N,N-di-Power alkylamino-lower alkyl; lower alkenyl; lower alkynyl; tri-lower alkylsilanyl-lower alkynyl; monohalo-, dihalo- or trihalo-lower alkyl; halogen; nitro; hydroxy; lower alkoxy; lower alkanoyloxy; isothiocyanato; phenyl that is unsubstituted or substituted by halogen, niko, trihalo-lower alkyl, hydroxy or by lower alkyl; thienyl; phenyl-lower alkoxy that is unsubstituted or substituted in the phenyl ring by halogen, nitro, trihalo-lower alkyl, hydroxy or by lower alkyl; carboxy; lower alkoxycarbonyl; carbamoyl; N-lower alkylcarbamoyl; N,N-di-lower alkyl-carbamoyl; cyano; amino; N-lower alkylamino; N,N-di-lower alkylamino; azido; benzoylamino that is unsubstituted or substituted in the benzene ring by halogen, nitro, tri-halo-lower alkyl, hydroxy or by lower alkyl; lower alkanoylamino; monohalo-, dihalo- or trihalo-lower alkylcarbonylamino; lower alkanesulfonylamino; trihalo-lower alkanesulfonylamino; lower alkylthio; lower alkylsulfinyl; lower alkanesulfonyl; pyrrol-1-yl; piperidin-1-yl; pyrrolidin-1-yl and lower alkanoyl, or two radicals R_3 together or two radicals R_4 together form lower alkylenedioxy;

the ring marked A is a heterocyclyl having from 5 to 9 ring atoms and having at least one saturated bond, it being possible for a further ring hetero atom selected from O and S to be present in addition to the bonding nitrogen atom;

the ring system marked B is a free or benzo-, thieno-, furo-, pyrrolo- or dihydropyrrolo-fused carbocyclic ring having from 5 to 9 carbon atoms that is fused to the ring A and may be unsaturated, partially saturated or fully saturated; and

the bond marked by a parallel dotted line between the ring systems marked A and B is either a single bond or a double bond;

and salts thereof where at least one salt-forming group is present.

[0003] The term "lower" used hereinabove and hereinbelow denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4, carbon atoms, and especially (unless indicated to the contrary) having 1 or 2 carbon atoms.

[0004] Where the compounds of formula I contain asymmetric centres, they may be in the form of mixtures of enantiomers, and where several asymmetric centres are present also in the form of diastereoisomeric mixtures; when double bonds are present, cis/trans isomers are possible. The compounds of formula I are preferably in the form of pure isomers.

[0005] Carbon atoms the substituents of which are not otherwise defined are bonded to hydrogen atoms; where the number of substituents is variable, a carbon atom will have as many substituents and hydrogen atoms as will result in the carbon atom in question being neutral and having a complete electron octet.

[0006] Lower alkyl is preferably n-butyl, n-propyl, isopropyl, ethyl or especially methyl.

[0007] Halogen is bromine, iodine or preferably fluorine or especially chlorine.

[0008] Monohalo-, dihalo- or trihalo-lower alkyl is especially trifluoromethyl.

[0009] Lower alkoxy is especially methoxy.

[0010] Monohalo-, dihalo- or trihalo-lower alkyl is especially monofluoro-, difluoro- or (especially) trifluoro-methyl.

[0011] Lower alkoxycarbonyl-methoxy is especially methoxycarbonyl-methoxy.

[0012] Amino-lower alkyl is especially aminomethyl.

[0013] Phenyl-substituted phenyl R_1 or R_2 is, for example, biphenylyl, especially 4-biphenylyl.

[0014] Lower alkanoylamino is especially acetylamino, propionylamino, n-butyrylamino or isobutyrylamino.

[0015] Lower alkoxycarbonylamino is especially methoxycarbonylamino or more especially tert-butoxycarbonylamino.

[0016] Phenyl-lower alkoxycarbonylamino is preferably benzyloxycarbonylamino.

[0017] Furoyl is especially furan-2-carbonyl.

[0018] Thienylcarbonyl is especially thienyl-2-carbonyl.

[0019] Lower alkylamino is, for example, propylamino, ethylamino or especially methylamino.

[0020] N,N-Di-lower alkylamino is especially dimethylamino.

[0021] Lower alkanoyloxy is especially acetoxy.

[0022] Lower alkoxycarbonyl is especially tert-butoxycarbonyl or more especially methoxycarbonyl.

[0023] N-Lower alkyl-carbamoyl is, for example, N-methylcarbamoyl, N-(n-butyl)-carbamoyl or N-(2-methyl-but-1-yl)-carbamoyl.

[0024] N,N-Di-lower alkyl-carbamoyl is, for example, N,N-dimethyl-carbamoyl.

[0025] N-(N',N'-Di-lower alkylamino-methylidene)-amino is especially N-(N',N'-dimethylaminomethylidene)-amino.

[0026] N-((N',N'-Di-lower alkylamino)-(lower alkyl)methylidene)-amino ist especially N-((N',N'-dimethylamino)-(isopropylamino)methylidene)-amino.

[0027] N^3-Lower alkylureido is especially N^3-methylureido (CH_3-NH-(C=O)-NH-).

[0028] N^3,N^3-Di-lower alkylureido is especially N^3, N^3-dimethylureido ([$(CH_3)_2$-N-(C=O)-NH-).

[0029] N^3-Lower alkylthioureido is especially N^3-methylthioureido (CH_3-NH-(C=S)-NH-).

[0030] N^3,N^3-Di-lower alkylthioureido is especially N^3, N^3-dimethylthioureido ([$(CH_3)_2$-N-(C=S)-NH-).

[0031] Lower alkanesulfonylamino is especially N-methanesulfonylamino (CH_3-(S{=O}$_2$-NH-).

[0032] Benzene- or naphthalene-sulfonylamino that is unsubstituted or lower alkyl-substituted at the benzene or naphthalene ring is especially 4-toluenesulfonylamino or benzenesulfonylamino.

[0033] Substituted phenyl R_1 or R_2 may carry one or more substituents, but preferably not more than 3 substituents, which may be identical or different from one another. Preferably, substituted phenyl R_1 or R_2 carries only one substituent in the ortho-position or, preferably, in the meta- or para-position. Substituted phenyl R_1 or R_2 is preferred to unsubstituted phenyl.

[0034] Unsubstituted or halo- or lower alkyl-substituted pyridyl is especially 2-pyridyl.

[0035] N-Benzyl-pyridonium is especially N-benzyl-pyridonium-2-yl.

[0036] Naphthyl is, for example, 2-naphthyl.

[0037] Lower alkanoyl is, for example, isobutyryl, butyryl, propionyl or especially acetyl.

[0038] Amino-lower alkyl is especially 3-aminopropyl.

[0039] N-Lower alkyl-amino-lower alkyl is especially 3-(N-methylamino)-propyl.

[0040] N,N-Di-lower alkylamino-tower alkyl is especially 3-(N,N-dimethylamino)-propyl.

[0041] Lower alkenyl has preferably from 2 to 7, especially from 2 to 4, carbon atoms and is preferably vinyl, prop-1-enyl or prop-2-enyl (allyl).

[0042] Lower alkenyloxy is, for example, vinyloxy, prop-1-enyloxy or prop-2-enyloxy (allyloxy).

[0043] Substituted lower alkyl R_1 or R_2 may carry one or more, but preferably not more than 3, substituents, which may be identical or different. Preferably, substituted lower alkyl R_1 or R_2 carries only one substituent

[0044] Lower alkyl substituted by phenylamino or phenyl that is unsubstituted or substituted in the phenyl moiety by halogen, lower alkyl, hydroxy, lower alkanoyloxy, lower alkoxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, amino, amino-lower alkyl, lower alkanoylamino, lower alkylamino, N;N-di-lower alkylamino or by trifluoromethyl is especially methyl substituted in that manner, and is preferably anilino-methyl or 4-methoxyanilino-methyl, or 3- or 4-aminophenyl-methyl.

[0045] Lower alkyl R_1 or R_2 substituted by a radical of the formula R_5-S(O_q)- wherein R_5 is lower alkyl and q is 0,1 or 2 is especially methanesulfonyl-methyl.

[0046] An alkylene chain having from 2 to 5 carbon atoms that is formed by R_1 and R_2 together and is unsubstituted or substituted by lower alkyl is preferably propylene or butylene.

[0047] Preference is given to compounds of formula I wherein R_1 and R_2 are the other radicals mentioned with the exception of an unsubstituted or substituted alkylene chain.

[0048] Preferably the two radicals R_1 and R_2 are each independently of the other lower alkyl, or R_2 is unsubstituted or substituted phenyl, as defined above, while R_1 is hydrogen or also lower alkyl, especially methyl. In especially preferred compounds of formula I, R_1 is methyl and R_2 is methyl; or R_1 is hydrogen or also methyl and R_2 is phenyl that is unsubstituted or substituted especially by amino, nitro or by methoxy, especially 4-aminophenyl, 4-nitrophenyl or 4-methoxyphenyl.

[0049] In heterocyclyl of formula IA bonded via a ring nitrogen atom, m and n are each independently of the other from 0 to 3; preferably m is 0 or 1 and n is from 0 to 3; and especially: n + m = 0 to 3, and more especially: m = 0 and n = 0 or 1.

[0050] Lower alkynyl is especially C_2-C_7alkynyl, preferably C_2-C_4alkynyl, such as ethynyl.

[0051] Tri-lower alkylsilanyl-lower alkynyl is especially trimethylsilanylethynyl.

[0052] Phenyl that is unsubstituted or substituted by halogen, nitro, trihalo-lower alkyl, hydroxy or by lower alkyl contains one or more, especially 3, but preferably one, of the mentioned substituents which can be selected independently of one another. Unsubstituted phenyl is preferred.

[0053] Thienyl is especially 2-thienyl.

[0054] Phenyl-lower alkoxy that is unsubstituted or substituted in the phenyl ring by halogen, nitro, trihalo-lower alkyl, hydroxy or by lower alkyl is especially benzyloxy.

[0055] Benzoylamino that is unsubstituted or substituted in the benzene ring by halogen, nitro, tri-halo-lower alkyl, hydroxy or by lower alkyl is especially unsubstituted benzoylamino.

[0056] Monohalo-, dihalo- or trihalo-lower alkylcarbonylamino is especially trifluoroacetylamino.

[0057] Trihalo-lower alkanesulfonylamino is especially trifluoromethanesulfonylamino.

[0058] Lower alkylthio is especially methylthio.

[0059] Lower alkylsulfinyl (lower alkyl-(S=O)-) is especially methyl- or ethyl-sulfinyl.

[0060] Lower alkanesulfonyl is preferably methanesulfonyl.

[0061] Lower alkylenedioxy formed by two radicals R_3 together or two radicals R_4 together is preferably bonded to

two vicinal ring atoms and is especially methylenedioxy. Lower alkylenedioxy is especially formed by two radicals R_4.

[0062] The ring marked A is a heterocyclyl having from 5 to 9 ring atoms and having at least one saturated bond, it being possible for a further ring hetero atom selected from O and S to be present in addition to the bonding nitrogen atom; preference is given to a corresponding 5-to 8-membered ring that does not contain a further hetero atom in addition to the bonding nitrogen atom, for example 2,3-dihydropyrrol-1-yl, 1,2,3,4-tetrahydropyridin-1-yl, 2,3,4,5-tetrahydroazepin-1-yl or 1,2,3,4,5,6-hexahydroazocin-1-yl.

[0063] The ring system marked B is a free or benzo-, thieno-, furo-, pyrrolo- or dihydropyrrolo-fused carbocyclic ring having from 5 to 9, preferably 6, carbon atoms that is fused to the ring A (via two vicinal atoms completing the ring) and may be unsaturated, partially saturated or fully saturated, and is especially benzo, naphtho, pyrrolo-fused benzo or 2,3-dihydropyrrolofused benzo.

[0064] Q is especially 2,3-dihydroindol-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl, 1,2,3,4,5,6-hexahydrobenzo[b]azocin-1-yl, 2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl, 1,2,3,5-tetrahydropyrrolo[2,3-f]indol-1-yl or 1,2,3,5,6,7-hexahydropyrrolo[2,3-f]indol-1-yl, each of which is unsubstituted or substituted by from 1 to 3 radicals R_3 or R_4 or R_3 and R_4 selected independently of one another from lower alkyl, N,N-di-lower alkylamino-lower alkyl, lower alkynyl, tri-lower alkylsilanyl-lower alkynyl, halogen, nitro, hydroxy, lower alkoxy, isothiocyanato, unsubstituted phenyl, unsubstituted phenyl-lower alkoxy, carboxy, lower alkoxycarbonyl, amino, azido, lower alkanoylamino, trihalo-lower alkylcarbonylamino, pyrrol-1-yl and pyrrolidih-1-yl or substituted by lower alkylenedioxy formed by two radicals R_4 together and is bonded to two vicinal ring atoms; Q is especially 2,3-dihydroindol-1-yl, 6-chloro-2,3-dihydroindol-1-yl, 6-bromo-2,3-dihydroindol-1-yl, 6-methyl-2,3-dihydroindol-1-yl or 1,2,3,4-tetrahydroquinolin-1-yl.

[0065] The bond marked by a parallel dotted line between the ring systems marked A and B is either a single bond or a double bond, preferably a double bond.

[0066] Salts of compounds of formula I are especially acid addition salts with organic or inorganic acids, especially the pharmaceutically acceptable, non-toxic salts. Suitable inorganic salts are, for example, carbonic acid (preferably in the form of carbonates or bicarbonates); hydrohalic acids, such as hydrochloric acid; sulfuric acid; or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2-hydroxybutyric acid, gluconic acid, glucosemonocarboxylic acid, fumaric add, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids, such as glutamic acid, aspartic acid, N-methylglycine, acetylaminoacetic acid, N-acetylasparagine or N-acetylcysteine, pyruvic acid, acetoacetic acid, phosphoserine, 2- or 3-glycerophosphoric acid, glucose-6-phosphoric acid, glucose-1-phosphoric acid, fructose-1,6-bisphosphoric acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 1- or 3-hydroxynaphthyl-2-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, glucuronic acid, galacturonic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalenedisulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propylsultamic acid, or other organic protonic acids, such as ascorbic acid.

[0067] Compounds of formula I that carry at least one free carboxy group can form internal salts or metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts or ammonium salts with ammonia or - suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethylpiperidine or N,N'-dimethylpiperazine.

[0068] For the purposes of isolation or purification it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. Only the salts that are pharmaceutically acceptable and non-toxic (at the doses in question) are used therapeutically and they are therefore preferred.

[0069] As a result of the close relationship between the novel compounds (especially of formula I) in free form and in the form of their salts, including those salts which can be used as intermediates, for example in the purification of the novel compounds or for the identification thereof, hereinabove and hereinbelow any reference to the free compounds should be understood as including also the corresponding salts, and solvates thereof, for example hydrates, as appropriate and expedient

[0070] The compounds of formula I exhibit valuable pharmacologically acceptable properties. In particular, they exhibit specific inhibitory actions that are of pharmacological interest. They act especially as inhibitors of tyrosine protein kinase and/or (further) as inhibitors of serine/threonine protein kinases; they exhibit, for example, potent inhibition of the tyrosine kinase activity of the receptor for the epidermal growth factor (EGF) and the c-erbB2 kinase. Those receptor-specific enzyme activities play a key role in signal transmission in a large number of mammalian cells, including human cells, especially epithelial cells, cells of the immune system and cells of the central and peripheral nervous system. For example, the EGF-induced activation of the receptor-associated tyrosine protein kinase (EGF-R-PTK) in

various cell types is a prerequisite for cell division and thus for the proliferation of the cell population. The administration of EGF-receptor-specific tyrosine kinase inhibitors therefore inhibits the reproduction of the cells. The same is true analogously of the other protein kinases mentioned hereinabove and hereinbelow.

[0071] The inhibition of the EGF-receptor-specific tyrosine protein kinase (EGF-R-PTK) can be demonstrated using known methods, for example using the receombinant intracellular domain of the EGF receptor (EGF-R ICD; see, for example, E. McGlynn *et al.*, Europ. J. Biochem. 207, 265-275 (1992)). The compounds of formula I inhibit the enzyme activity in comparison with the control without inhibitor by 50 % (IC_{50}), for example in a concentration of from 0.001 to 20 μM, especially from 0.01 to 5 μM.

[0072] The action of the compounds of formula I on the EGF-stimulated cellular tyrosine phosphorylation in the EGF receptor can be determined in the human A431 epithelium carcinoma cell line by means of an ELISA that is described in U. Trinks et *al.,* J. Med. Chem. 37(7), 1015-1027 (1994). In that test (EGFR-ELISA) the compounds of formula I exhibit inhibition at concentrations in the nanomolar to micromolar range.

[0073] The stimulation of dormant BALB/c3T3 cells by EGF rapidly induces the expression of c-fos mRNA. Pretreatment of the cells with a compound of formula I prior to the stimulation with EGF can inhibit the c-fos expression. That test procedure is likewise described in U. Trinks *et al.*, J. Med. Chem. 37(7), 1015-1027 (1994).

[0074] In the micromolar range also, the compounds of formula I also exhibit, for example, inhibiton of the cell growth of EGF-dependent cell lines, for example the epidermoid BALB/c mouse keratinocyte cell line (see Weissmann, B.A., and Aaronson, S.A., Cell 32, 599 (1983)) or the A431 cell line, which are acknowledged as useful standard sources of EGF-dependent epithelial cells (see Carpenter, G., and Zendegni, J. Anal. Biochem. 153, 279-282 (1985)). In a known test method (see Meyer *et al.*, Int. J. Cancer 43, 851 (1989)) the inhibitory action of the compounds of formula I is determined briefly as follows: BALB/MK cells (10 000/microtitre plate well) are transferred to 96-well microtitre plates. The test compounds (dissolved in DMSO) are added in a series of concentrations (dilution series), so that the final concentration of DMSO is no greater than 1 % (v/v). After the addition, the plates are incubated for three days, during which time the control cultures without test compound are able to undergo at least three cell division cycles. The growth of the MK cells is measured by means of methylene blue staining: after the incubation the cells are fixed with glutaraldehyde, washed with water and stained with 0.05% methylene blue. After a washing step, the stain is eluted with 3 % HCl and the optical density per well of the microtitre plate is measured using a Titertek multiskan at 665 nm. IC_{50} values are determined by means of a computer-aided system using the formula

$$IC_{50} = [(OD_{test} - OD_{start})/(OD_{control} - OD_{start})] \times 100.$$

[0075] The IC_{50} value in those experiments is defined as that concentration of the test compound in question which results in a 50 % decrease in the number of cells in comparison with the control without inhibitor. The compounds of formula I exhibit inhibitory actions in the micromolar range, especially having an IC_{50} of approximately from 0.1 to 50 μM.

[0076] The compounds of formula I are also capable of inhibiting the growth of tumour cells *in vivo,* as shown, for example, by the test described below: the test is based on the inhibition of the growth of the human epidermoid carcinoma A431 (ATCC No. CRL 1555; American Type Culture Collection, Rockville, Maryland, USA; see Santon, J.B., *et al.*, Cancer Research 46, 4701-4705 (1986) and Ozawa, S., *et al.*, Int. J. Cancer 40, 706-710 (1987)), which is transplanted into female BALB/c naked mice (Bomholtgard, Denmark). That carcinoma exhibits a growth which correlates with the extent of the expression of the EGF receptor. In the experiment, tumours of about 1 cm^3 volume grown *in vivo* are surgically removed from experimental animals under sterile conditions. Those tumours are comminuted and suspended in 10 volumes (w/v) of phosphate-buffered saline. The suspension is injected s.c. into the left flank of the animals (0.2 ml/mouse in phosphate-buffered saline). Alternatively, 1 x 10^6 cells from an *in vitro* culture in 0.2 ml of phosphate-buffered saline can be injected. The treatment with the test compounds of formula I is begun 5 or 7 days after transplantation when the tumours have attained a diameter of 4-5 mm. The test compound in question is administered (in different doses for different groups of animals) once daily for 15 successive days. The tumour growth is determined by measuring the diameter of the tumours along three axes that are perpendicular to one another. The tumour volumes are calculated using the known formula p x L x D^2/6 (see Evans, B.D., *et al.*, Brit. J. Cancer 45, 466-468 (1982)). The results are expressed as treatment/control percentages (T/C x 100 = T/C%).

[0077] In addition to or instead of inhibiting the EGF receptor tyrosine protein kinase, the compounds of formula I also inhibit other tyrosine protein kinases that are involved in the signal transmission mediated by trophic factors, for example the abl kinase, such as especially the v-abl kinase (IC_{50}, for example, from 0.01 to 5 μM), kinases of the src kinase family, such as especially the c-src kinase (IC_{50}, for example, from 0.01 to 10 μM), and also lck and fyn; other kinases of the EGF family, for example the c-erbB2 kinase (HER-2), the c-erbB3 kinase, the c-erbB4 kinase; members of the PDGF tyrosine protein kinase family, for example the PDGF receptor, CSF-1, Kit, VEGF-R and FGF-R; and the insulin-like growth factor receptor kinase (IGF-1-kinase), and also serine/threonine kinases, for example protein kinase C, all of which play a part in growth regulation and transformation in mammal cells, including human cells. Finally, the

compounds of formula I can also be used in the inhibition of angiogenesis.

[0078] The above-mentioned inhibition of the v-abl tyrosine kinase is determined in accordance with the methods of N. Lydon *et al.*, Oncogene Research 5, 161-173 (1990) and J. F. Geissler *et al.*, Cancer Research 52, 4492-4498 (1992), with [Val^5]-angiotensin II and [γ-^{32}P]-ATP being used as substrates.

[0079] The inhibition of the c-erbB2 tyrosine kinase (HER-2) can be determined, for example, analogously to the method used for EGF-R-PTK (see C. House *et al.,* Europ. J. Biochem. 140, 363-367 (1984)). The c-erbB2 kinase can be isolated and its activity determined in accordance with protocols known *per se*, for example according to T. Akiyama et *al.,* Science 232, 1644 (1986)).

[0080] The compounds of formula I that inhibit the tyrosine kinase activity of the receptor for the epidermal growth factor (EGF) or, further, the other tyrosine protein kinases mentioned or also serine/threonine kinases can therefore be used, for example, in the treatment of benign or malignant tumours (for example carcinoma of the kidneys, liver, adrenal glands, bladder, breast, stomach, ovaries, colon, rectum, prostate, pancreas, lungs, vagina or thyroid, sarcoma, glioblastomas and numerous tumours of the neck and head). They are able to bring about the regression of tumours and to prevent the formation of tumour metastases and the growth of (also micro-)metastases. More especially they can be used in epidermal hyperproliferation (psoriasis), in prostate hyperplasia, in the treatment of neoplasias, especially of epithelial character, for example mammary carcinoma, and in leukaemias. It is also possible to use the compounds of formula I in the treatment of diseases of the immune system insofar as several or, especially, individual tyrosine protein kinases and/or (further) serine/threonine protein kinases are involved; the compounds of formula I can be used also in the treatment of diseases of the central or peripheral nervous system where signal transmission by at least one tyrosine protein kinase and/or (further) serine/threonine protein kinase is involved.

[0081] Generally the present invention relates also to the use of the compounds of formula I in the inhibition of the said protein kinases.

[0082] The compounds according to the invention can be used both on their own and in combination with other pharmacologically active substances, for example together with inhibitors of enzymes of polyamine biosynthesis, inhibitors of protein kinase C, inhibitors of other tyrosine kinases, cytokines, negative growth regulators, for example TGF-β or IFN-β, arbmatase inhibitors, antioestrogens and/or cytostatics.

[0083] In the preferred subjects of the invention mentioned below, where appropriate and expedient it is possible to use the more specific definitions mentioned at the beginning in place of more general definitions.

[0084] Preference is given to a compound of formula I wherein

R_1 and R_2 are each independently of the other
lower alkyl; monohalo-, dihalo- or trihalo-lower alkyl; lower alkoxy; phenyl that is unsubstituted or substituted by halogen, monohalo-, dihalo- or trihalo-lower alkyl, carbamoyl-methoxy, carboxy-methoxy, benzyloxycarbonylmethoxy, lower alkoxycarbonylmethoxy, phenyl, amino, amino-lower alkyl, lower alkanoylamino, lower alkoxycarbonylamino, phenyl-lower alkoxycarbonylamino, furoyl, thienylcarbonyl, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, lower alkoxy, lower alkanoyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, N-(N',N'-di-lower alkylaminomethylidene)-amino, N-((N',N'-di-lower alkylamino)-(lower alkyl)-methylidene)-amino, guanidino, ureido, N^3-lower alkylureido, N^3,N^3-di-lower alkylureido, thioureido, N^3-lower alkylthioureido, N^3,N^3-di-lower alkylthioureido, lower alkanesulfonylamino, benzene- or naphthalene-sulfonylamino that is unsubstituted or lower alkyl-substituted at the benzene or naphthalene ring, azido or by nitro; hydrogen; unsubstituted or halo- or lower alkyl-substituted pyridyl; N-benzyl-pyridonium; naphthyl; cyano; carboxy; lower alkoxycarbonyl; carbamoyl; N-lower alkyl-carbamoyl; N,N-di-lower alkylcarbamoyl; N-benzyl-carbamoyl; formyl; lower alkanoyl; lower alkenyl; lower alkenyloxy; or lower alkyl substituted by halogen, amino, lower alkylamino, piperazino, di-lower alkylamino, phenylamino or phenyl (each unsubstituted or substituted in the phenyl moiety by halogen, lower alkyl, hydroxy, lower alkanoyloxy, lower alkoxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, amino, amino-lower alkyl, lower alkanoylamino, lower alkylamino, N,N-di-lower alkylamino or by trifluoromethyl), hydroxy, lower alkoxy, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, mercapto or by a radical of the formula R_5-S(O_q)- wherein R_5 is lower alkyl and q is 0, 1 or 2, and

Q is a radical of formula IA selected from 2,3-dihydroindol-1-yl; and preferably 1,2,3,4-tetrahydroquinolin-1-yl, 2,3,4,5-tetrahydro-1H-benzo[b]acepin-1-yl, 1,2,3,4,5,6-hexahydrobenzo[b]azocin-1-yl, 2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl, 1,2,3,5-tetrahydropyrrolo[2,3-f]-indol-1-yl and 1,2,3,5,6,7-hexahydro-pyrrolo[2,3-flindol-1-yl; each of the mentioned radicals being unsubstituted or substituted by from 1 to 3 (i.e. m + n = 0 to 3) radicals R_3 or R_4 or R_3 and R_4 selected independently of one another from lower alkyl, N,N-di-lower alkylamino-lower alkyl, lower alkynyl, tri-lower alkylsilanyl-lower alkynyl, halogen, nitro, hydroxy, lower alkoxy, isothiocyanato, unsubstituted phenyl, unsubstituted phenyl-lower alkoxy, carboxy, lower alkoxycarbonyl, amino, azido, lower alkanoylamino, trihalo-lower alkylcarbonylamino, pyrrol-1-yl and pyrrolidin-1-yl or substituted by lower alkylenedioxy that is

formed by two radicals R_4 together and is bonded to two vicinal ring atoms; Q is especially 2,3-dihydroindol-1-yl, 6-chloro-2,3-dihydroindol-1-yl, 6-bromo-2,3-dihydroindol-1-yl, 6-methyl-2,3-dihydroindol-1-yl or more especially 1,2,3,4-tetrahydroquinolin-1-yl;

or a salt thereof where at least one salt-forming group is present.

[0085] Great preference is given to a compound of formula I wherein

R_1 and R_2 are each independently of the other selected from hydrogen, lower alkyl, such as methyl, and phenyl that is unsubstituted or substituted by halogen, monohalo-, dihalo- or trihalo-lower alkyl, carbamoyl-methoxy, carboxy-methoxy, benzyloxycarbonyl-methoxy, lower alkoxycarbonyl-methoxy, phenyl, amino, amino-lower alkyl, lower alkanoylamino, lower alkoxycarbonylamino, phenyl-lower alkoxycarbonylamino, furoyl, thienylcarbonyl, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, lower alkanoyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, N-(N',N'-di-lower alkylaminomethylidene)-amino, N-((N',N'-di-lower alkylamino)-(lower alkyl)-methylidene)amino, guanidino, ureido, N^3-lower alkylureido, N^3,N^3-di-lower alkylureido, thioureido, N^3-lower alkylthioureido, N^3,N^3-di-lower alkylthioureido, lower alkanesulfonylamino, benzene- or naphthalene-sulfonylamino that is unsubstituted or lower alkyl-substituted at the benzene or naphthalene ring, azido or by nitro, and

Q is a radical of formula IA selected from 2,3-dihydroindol-1-yl; and preferably 1,2,3,4-tetrahydroquinolin-1-yl, 2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl, 1,2,3,4,5,6-hexahydrobenzo[b]azocin-1-yl, 2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl, 1,2,3,5-tetrahydropyrrolo[2,3-f]indol-1-yl and 1,2,3,5,6,7-hexahydro-pyrrolo[2,3-f]indol-1-yl; each of the mentioned radicals being unsubstituted or substituted by from 1 to 3 radicals R_3 or R_4 or R_3 and R_4 selected independently of one another from lower alkyl, N,N-di-lower alkylamino-lower alkyl, lower alkynyl, tri-lower alkylsilanyl-lower alkynyl, halogen, nitro, hydroxy, lower alkoxy, isothiocyanato, unsubstituted phenyl, unsubstituted phenyl-lower alkoxy, carboxy, lower alkoxycarbonyl, amino, azido, lower alkanoylamino, trihalo-lower alkylcarbonylamino, pyrrol-1-yl and pyrrolidin-1-yl or substituted by lower alkylenedioxy that is formed by two radicals R_4 together and is bonded to two vicinal ring atoms; Q is especially 2,3-dihydroindol-1-yl, 6-chloro-2,3-dihydroindol-1-yl, 6-bromo-2,3-dihydroindol-1-yl, 6-methyl-2,3-dihydroindol-1-yl or especially 1,2,3,4-tetrahydroquinolin-1-yl;

or a salt thereof.

[0086] Special preference is given to a compound of formula I wherein

either the two radicals R_1 and R_2 are each independently of the other lower alkyl, preferably each methyl;

or R_1 is hydrogen and R_2 is phenyl that is unsubstituted or especially substituted by amino, nitro or by methoxy, especially 4-aminophenyl, 4-nitrophenyl or 4-methoxyphenyl; and

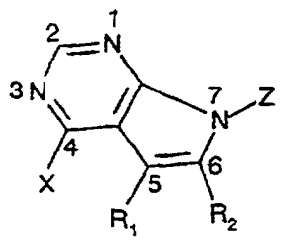
Q is 2,3-dihydroindol-1-yl, 6-chloro-2,3-dihydroindol-1-yl, 6-bromo-2,3-dihydroindol-1-yl, 6-methyl-2,3-dihydroindol-1-yl or especially 1,2,3,4-tetrahydroquinolin-1-yl;

or a salt thereof.

[0087] Greatest preference is given to the compounds of formula I described in the Examples and the pharmaceutically acceptable salts thereof.

[0088] The compounds of formula I and their salts are prepared in accordance with processes known *per se.* The process according to the invention is as follows:

a) a pyrrolo[2,3-d]pyrimidine derivative of formula II



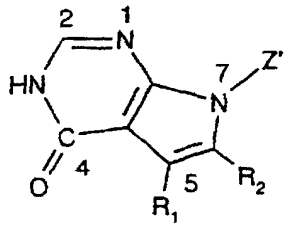
(II),

wherein X is a suitable leaving group, Z is hydrogen or 1-aryl-lower alkyl and the other substituents are as defined above for compounds of formula I, free functional groups present in the radicals R_1 and R_2 being protected if necessary by readily removable protecting groups, is reacted with an aza compound of formula III

Q-H (III),

wherein Q is as defined above for compounds of formula I, free functional groups present in the radical Q being protected if necessary by readily removable protecting groups, and any protecting groups and, if present, the 1-aryl-lower alkyl radical Z are removed, or

b) a pyrrolo[2,3-d]pyrimidin-4-one derivative of formula IV



(IV),

wherein Z' is 1-aryl-lower alkyl and R_1 and R_2 are as defined above for compounds of formula I, free functional groups present in the radicals R_1 and R_2 being protected if necessary by readily removable protecting groups, is reacted in the presence of a dehydrating agent and a tertiary amine (which is preferably in the form of a salt with a strong acid) with an aza compound of the above formula III and any protecting groups present are removed;
and, if desired, after carrying out one of the process variants a) and b), a compound of formula I is converted into a different compound of formula I; and/or, if necessary for the preparation of a salt, a resulting free compound of formula I is converted into a salt or, if necessary for the preparation of a free compound, a resulting salt of a compound of formula I is converted into the free compound; or an obtainable salt of a compound of formula I is converted into a different salt of a compound of formula I.

Detailed description of the preferred process steps

[0089] The above processes are described in more detail below (see also German Offenlegungsschrift No. 30 36 390, published on 13th May 1982, and A. Jorgensen *et al.*, J. Heterocycl. Chem. 22, 859 [1985]). In the following more detailed description, unless otherwise indicated the radicals R_1, R_2, Q, R_3 and R_4 and the variables m and n are as defined for compounds of formula I.

General remarks:

[0090] The end products of formula I may contain substituents that can be used also as protecting groups in starting materials for the preparation of other end products of formula 1. Within the scope of this text, unless the context indicates otherwise the term "protecting group" is therefore used to denote only a readily removable group that is not a constituent of the desired end product of formula I in question.

Process a)

[0091] In the compound of formula II, a suitable leaving group X is preferably halogen, such as bromine, iodine or especially chlorine. 1-Aryl-lower alkyl Z is preferably 1-phenyl-lower alkyl, such as especially 1-phenylethyl or more especially benzyl.

[0092] Free functional groups present in the radicals R_1 and R_2 and also Q, which are if necessary protected by readily removable protecting groups, are especially amino or lower aikylamino, or also hydroxy.

[0093] Protecting groups and the methods by which they are introduced and removed are described, for example, in "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973, and in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Vol. 15/1, Georg-Thieme-Verlag, Stuttgart 1974, and in Theodora W. Greene, "Protective Groups in Organic Synthesis, John Wiley & Sons, New York 1981. It is characteristic of protecting groups

that they can be removed readily, that is to say without undesirable secondary reactions taking place, for example by solvolysis, reduction, photolysis or under physiological conditions.

[0094] A protected amino group may be, for example, in the form of a readily cleavable acylamino, arylmethylamino, etherified mercaptoamino or 2-acyl-lower alk-1-enylamino group.

[0095] In such an acylamino group, acyl is, for example, the acyl radical of an organic carboxylic acid having, for example, up to 18 carbon atoms, especially an unsubstituted or substituted, for example halo- or aryl-substituted, alkanecarboxylic acid or an unsubstituted or substituted, for example halo-, lower alkoxy- or nitro-substituted, benzoic acid, or a carbonic acid semiester. Such acyl groups are, for example, lower alkanoyl, such as fomlyl, acetyl or propionyl, halo-lower alkanoyl, such as 2-haloacetyl, especially 2-chloro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloroacetyl, unsubstituted or substituted, for example halo-, lower alkoxy- or nitro-substituted, benzoyl, for example benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl or 4-nitrobenzoyl, or lower alkoxycarbonyl that is branched in the 1-position of the lower alkyl radical or suitably substituted in the 1- or 2-position, especially tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl, arylmethoxycarbonyl having one or two aryl radicals which are preferably phenyl that is unsubstituted or mono- or poly-substituted, for example, by lower alkyl, especially tert-lower alkyl, such as tert-butyl, lower alkoxy, such as methoxy, hydroxy, halogen, such as chlorine, and/or by nitro, such as unsubstituted or substituted benzyloxycarbonyl, for example 4-nitrobenzyloxycarbonyl, or substituted diphenylmethoxycarbonyl, for example benzhydryloxycarbonyl or di(4-methoxyphenyl)-methoxycarbonyl, aroylmethoxycarbonyl wherein the aroyl group is preferably benzoyl that is unsubstituted or substituted, for example, by halogen, such as bromine, for example phenacyloxycarbonyl, 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl, or 2-(trisubstituted silyl)-ethoxycarbonyl wherein the substituents are each independently of the others an unsubstituted or substituted, for example lower alkyl-, lower alkoxy-, aryl-, halo- or nitro-substituted, aliphatic, araliphatic, cycloaliphatic or aromatic hydrocarbon radical having up to 15 carbon atoms, such as corresponding unsubstituted or substituted lower alkyl, phenyl-lower alkyl, cycloalkyl or phenyl, for example 2-tri-lower alkylsilyl-ethoxycarbonyl, such as 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methyl-silyl)-ethoxycarbonyl, or 2-triarylsilylethoxycarbonyl, for example 2-triphenylsilylethoxycarbonyl.

[0096] In an arylmethylamino group, which is a mono-, di- or especially tri-arylmethylamino group, the aryl radicals are especially unsubstituted or substituted phenyl-radicals. Such-groups are, for example, benzyl-, diphenylmethyl- or especially trityl-amino.

[0097] An etherified mercapto group in an amino group protected by such a radical is especially arylthio or aryl-lower alkylthio wherein aryl is especially phenyl that is unsubstituted or substituted, for example by lower alkyl, such as methyl or tert-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or by nitro. One such amino-protecting group is, for example, 4-nitrophenylthio.

[0098] In a 2-acyl-lower alk-1-en-1-yl radical that can be used as an amino-protecting group, acyl is, for example, the corresponding radical of a lower alkanecarboxylic acid, of a benzoic acid that is unsubstituted or substituted, for example, by lower alkyl, such as methyl or tert-butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or by nitro, or especially of a carbonic acid semiester, such as a carbonic acid lower alkyl semiester.
Such protecting groups are especially 1-lower alkanoyl-prop-1-en-2-yl, for example 1-acetyl-prop-1-en-2-yl, or 1-lower alkoxycarbonyl-prop-1-en-2-yl, such as 1-ethoxycarbonyl-prop-1-en-2-yl.

[0099] Preferred amino-protecting groups are acyl radicals of carbonic acid semiesters, especially tert-butyloxycarbonyl, benzyloxycarbonyl that is unsubstituted or substituted, for example as indicated, for example 4-nitro-benzyloxycarbonyl, or diphenylmethoxycarbonyl, or 2-halo-lower alkoxycarbonyl, such as 2,2,2-trichloroethoxycarbonyl, and also trityl or formyl.

[0100] The reaction between the derivative of formula II and the aza compound of formula III is effected in suitable, inert polar solvents, especially alcohols, for example lower alkanols, such as methanol, propanol, isopropanol or especially ethanol or n-butanol. In some cases, the addition of a solubiliser, such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1 H)-pyrimidinone (DMPU), is advantageous. The reaction is effected at elevated temperatures, for example in a temperature range of from 70 to 150°C, preferably under reflux conditions. For the preparation of those compounds where a sterically hindered compound (for example a 2-lower alkyl-indoline) of formula III is used, it is preferable to use tert-butanol or an aprotic solvent, such as dimethylformamide, dimethylacetamide or N-methylpyrrolidin-2-one, as solvent. If necessary, a base is added, for example an alkali metal or alkaline earth metal carbonate or hydroxide, or a tertiary nitrogen base, such as pyridine, 2,6-lutidine, collidine, N-methylmorpholine, triethylamine, diisopropylethylamine, 4-dimethylaminopyridine or N,N-dimethylaniline.

[0101] If Z in the compound of formula II is 1-aryl-lower alkyl, that radical is removed in the resulting precursor of the compound of formula I (with Z in place of the hydrogen atom at the nitrogen atom). That is effected, for example, by treatment with protonic acids, such as hydrochloric acid, phosphoric acid or polyphosphoric acid, at preferred temperatures of from 20°C to 150°C and optionally in the presence of water (this is especially the preferred method for Z = 1-phenylethyl); or preferably by treatment with Lewis acids, especially $AlCl_3$, in an aromatic solvent, especially in benzene and/or toluene, at elevated temperature, especially under reflux [this is especially the preferred variant for Z =

benzyl; see also the analogous procedure in Chem. Pharm. Bull. 39(5), 1152 (1991)].

Removal of protecting groups

[0102] The removal of protecting groups that are not constituents of the desired end product of formula I is carried out in a manner known *per se,* for example by means of solvolysis, especially hydrolysis, alcoholysis or acidolysis, or by means of reduction, especially hydrogenolysis or chemical reduction, optionally stepwise or simultaneously. The removal is effected preferably in accordance with or analogously to the methods described in the standard works mentioned above.

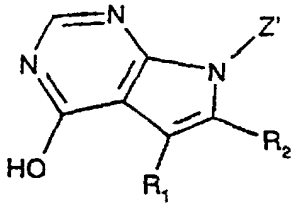
[0103] A protected amino group, for example, is freed in a manner known *per se* and, according to the nature of the protecting groups, in various ways, preferably by solvolysis or reduction. 2-Halo-lower alkoxycarbonylamino (where appropriate after conversion of a 2-bromo-lower alkoxycarbonylamino group into a 2-iodo-lower alkoxycarbonylamino group), aroylmethoxycarbonylamino or 4-nitrobenzyloxycarbonylamino can be cleaved, for example, by treatment with a suitable chemical reducing agent, such as zinc in the presence of a suitable carboxylic acid, such as aqueous acetic acid. Aroylmethoxycarbonylamino can be cleaved also by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate, and 4-nitrobenzyloxycarbonylamino also by treatment with an alkali metal dithionite, for example sodium dithionite. Unsubstituted or substituted diphenylmethoxycarbonylamino, tert-lower alkoxycarbonyiamino or 2-trisubstituted silylethoxycarbonylamino can be cleaved by treatment with a suitable acid, for example formic acid or trifluoroacetic acid; unsubstituted or substituted benzyloxycarbonylamino can be cleaved, for example, by means of hydrogenolysis, i.e. by treatment with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium catalyst; unsubstituted or substituted triarylmethylamino or formylamino can be cleaved, for example, by treatment with an acid, such as a mineral acid, for example hydrochloric acid, or an organic acid, for example formic, acetic or trifluoroacetic acid, where appropriate in the presence of water, and an amino group protected by an organic silyl group can be freed, for example, by means of hydrolysis or alcoholysis. An amino group protected by 2-haloacetyl, for example 2-chloroacetyl, can be freed by treatment with thiourea in the presence of a base, or with a thiolate salt, such as an alkali metal thiolate, of thiourea and subsequent solvolysis, such as alcoholysis or hydrolysis, of the resulting condensation product. An amino group protected by 2-substituted silylethoxycarbonyl can be converted into the free amino group also by treatment with a salt of hydrofluoric acid that yields fluoride anions.

Process b)

[0104] 1-Aryl-lower alkyl Z' in a compound of formula IV is especially 1-phenylethyl and also benzyl.

[0105] The compound of formula IV is in tautomeric equilibrium (lactam/lactim form), it being assumed that the lactam form (formula IV) predominates. Formula IV is used to represent the two possible forms of equilibrium.

[0106] The lactim form has the formula IVa



(IVa)

wherein the radicals are as defined for compounds of formula IV.

[0107] The dehydrating agent used is especially a strong chemical dehydrating agent, more especially phosphorus pentoxide (P_4O_{10}).

[0108] A suitable tertiary amine is especially ammonia substituted by three radicals selected independently of one another from alkyl, especially lower alkyl, such as methyl or ethyl, and cycloalkyl having from 3 to 7 carbon atoms, especially cyclohexyl, for example N,N-dimethyl-N-cyclohexylamine, N-ethyl-N,N-diisopropylamine or triethylamine, or also pyridine, N-methylmorpholine or 4-dimethylaminopyridine.

[0109] The tertiary amine is preferably in the form of a salt with a strong acid, preferably an inorganic acid, such as sulfuric acid, phosphoric acid or especially a hydrogen halide, such as hydrogen chloride.

[0110] The reaction between the pyrrolo-pyrimidinone of formula IV and the aza compound of formula III is effected at elevated temperature, for example at from 200 to 250°C.

Additional Process Steps

[0111] In the additional process steps, which are optional, functional groups of the starting compounds that are not intended to participate in the reaction may be unprotected or may be in protected form; for example they may be protected by one or more of the protecting groups mentioned above. The protecting groups may be removed from the end products, simultaneously or in sequence, in accordance with one of the methods mentioned under the heading "Removal of protecting groups".

[0112] The conversion of a compound of formula I into a different compound of formula I is effected especially by conversion of substituents in formula I.

[0113] For example, for the preparation of a compound of formula I wherein R_1 is dimethylaminomethyl and the other substituents are as defined above for compounds of formula I, a compound corresponding to formula I wherein R_1 is hydrogen and other substituents are as defined above for compounds of formula I, any further free functional groups present being protected if necessary by readily removable protecting groups, can be reacted with N,N-dimethyl-methyleneimmonium iodide and any protecting groups present removed. The reaction is carried out with the exclusion of moisture in a suitable inert solvent, for example a suitable ether, such as a cyclic ether, such as especially tetrahydrofuran, at elevated temperature, preferably under reflux.

[0114] For the preparation of a compound of formula I wherein at least one of the radicals R_1 and R_2 is hydroxy-substituted phenyl and/or wherein at least one of the radicals R_3 and R_4 is hydroxy and the other substituents are as defined above for compounds of formula I, it is also possible for a compound corresponding to formula I wherein at least one of the radicals R_1 and R_2 is lower alkoxy-substituted, especially methoxy-substituted, phenyl and/or wherein at least one of the radicals R_3 and R_4 is lower alkoxy and the other substituents are as defined above for compounds of formula I, any free functional groups present being protected if necessary by readily removable protecting groups, to be reacted with boron tribromide or aluminium(III) chloride, and any protecting groups present to be removed. The reaction is carried out with the exclusion of moisture in a suitable inert solvent, for example a suitable halogenated hydrocarbon, such as especially methylene chloride, at temperatures of approximately from -20°C to +50°C, preferably with ice-cooling or at room temperature.

[0115] For the preparation of a compound of formula I wherein at least one of the radicals R_1 and R_2 is amino-substituted amino and/or wherein at least one of the radicals R_3 and R_4 is amino and the other substituents are as defined above for compounds of formula I, a compound of formula I wherein at least one of the radicals R_1 and R_2 is nitro-substituted phenyl and/or wherein at least one of the radicals R_3 and R_4 is nitro and the other substituents are as defined above for compounds of formula I, any free functional groups present being protected if necessary by readily removable protecting groups, can be catalytically hydrogenated and any protecting groups present removed. The hydrogenation is preferably carried out under elevated pressure or especially at normal pressure in the presence of a suitable hydrogenation catalyst, such as especially Raney nickel, in an inert solvent or solvent mixture, such as especially a mixture of a suitable cyclic ether and a suitable lower alkanol, such as preferably a mixture of tetrahydrofuran and methanol, at temperatures of approximately from 0°C to +50°C, preferably at room temperature.

[0116] For the preparation of a compound of formula I wherein at least one of the radicals R_1 and R_2 is phenyl substituted by N-(N',N'-di-lower alkylaminomethylidene)-amino or by N-((N',N'-di-lower alkylamino)-(lower alkyl)-methylidene)amino and the other substituents are as defined above for compounds of formula I, a compound corresponding to formula I wherein at least one of the radicals R_1 and R_2 is amino-substituted phenyl and the other substituents are as defined above for compounds of formula I, any further free functional groups present being protected if necessary by readily removable protecting groups, can be reacted with a N,N-di-lower alkylformamide diethylacetal, especially N,N-dimethylformamide dimethylacetal, or N,N-di-lower alkyl-lower alkylcarboxylic acid amide diethylacetal, especially N,N-dimethylacetamide dimethylacetal, in an inert solvent, for example in toluene, and any protecting groups present removed.

[0117] Lower alkyl R_1 or R_2 substituted by a radical of the formula R_5-S(O_q)-, wherein R_5 is lower alkyl and q is 0, or lower alkylthio R_3 or R_4 can be converted into corresponding R_5-S(O_q)-wherein q is 1 or 2, that is into lower alkylsulfinyl or lower alkanesulfonyl, respectively, by oxidising the corresponding thio compounds, for example with hydrogen peroxide, a peracid, such as 3-chloroperbenzoic acid, performic acid or peracetic acid, an alkali metal peroxysulfate, such as potassium peroxymonophosphate, chromium trioxide or gaseous oxygen in the presence of platinum. The oxidation is carried out under conditions that are as mild as possible, using the stoichiometric amount of the oxidising agent in order to avoid overoxidation. Suitable solvents are especially methylene chloride, chloroform, acetone, tetrahydrofuran or tert-butyl methyl ether, and the temperature is preferably from -30 to 50°C, preferably in the range of from 18 to 28°C, for example at room temperature. For the preparation of sulfinyl compounds it is possible to use, preferably, milder oxidising agents, such as sodium or potassium metaperiodate, in a polar solvent, such as acetic acid or ethanol.

[0118] From compounds of formula I wherein R_1 and/or R_2 is phenyl substituted by cyano or by cyano-C_1-C_6alkyl it is possible to obtain the corresponding cyano-lower alkylphenyl compound by reduction, for example by catalytic hy-

drogenation, for example in the presence of Raney nickel or especially Raney-Ushibara nickel, in an alcohol, such as methanol, at preferred temperatures of from 20 to 100°C, preferably at about 90°C, elevated hydrogen pressures, for example from 1 to 15 MPa (about 10 to 150 atm), being preferred, or with a suitable complex hydride, such as lithium aluminium hydride in a suitable solvent, especially an ether, such as diethyl ether, preferably under reflux.

[0119] From compounds of formula I wherein R_1 and/or R_2 is cyano-substituted phenyl it is possible to obtain the corresponding amidines by aminolysis with ammonia or by a Pinner cleavage *via* the formation of imino esters (alkyl imidates) by the addition of dry hydrogen chloride to a mixture of the nitrile starting material and an alcohol and subsequent treatment with ammonia (see Chem. Ber. 10, 1889 (1877); Chem. Ber. 11, 4, 1475 (1878) or Chem. Ber. 16, 352, 1643 (1883)).

[0120] From compounds of formula I wherein R_1 and/or R_2 is amino-substituted lower alkyl or amino-substituted phenyl it is possible to obtain by acylation the corresponding compounds wherein the place of one or more of the amino groups has been taken by lower alkanoylamino or (in the case of amino-substituted phenyl as starting material) ureido, N^3-lower alkylureido, N^3,N^3-di-lower alkytureido, lower alkanesulfonylamino, or benzene- or naphthalene-sulfonylamino that is unsubstituted or lower alkyl-substituted at the benzene or naphthalene ring, by acylation under customary conditions. A suitable acylating agent is, for example, any corresponding suitable reagent that is suitable for the acylation of amino groups, for example a corresponding acyl halide, such as a bromide or chloride, a corresponding anhydride or mixed anhydride, a cyanate (for the preparation of ureido compounds), for example a corresponding alkali metal cyanate, or an isocyanate. N-Sulfonylation can be carried out with corresponding sulfonyl halides or anhydrides. The reactions take place in a solvent inert towards the reaction and at preferred temperatures in the range of from -20 to approximately 120°C, preferably at about room temperature.

[0121] For the conversion of hydroxy into carbamoyl or into carbamoyl substituted as indicated in the substituent definitions given above or into lower alkanoyloxy, corresponding acylating agents are suitable, for example corresponding halides, anhydrides or mixed anhydrides.

[0122] The reaction conditions are analogous to those given above for the acylation of amino groups. Acylation *in situ,* for example in the presence of condensation agents, such as carbodiimides, is also possible. For the introduction of carbamoyl or substituted carbamoyl it is also possible to use corresponding cyanates or alkyl isocyanates, typically in the presence of a suitable base.

[0123] For the conversion of at least one hydroxy or amino group as substituent in a compound of formula I into lower alkoxy, carbamoylmethoxy, carboxymethoxy, benzyloxycarbonyl-methoxy, lower alkoxycarbonylmethoxy or lower alkylamino, alkylation, preferably in the presence of a suitable base, is suitable. A suitable alkylating agent is, for example, a corresponding alkyl halide which is used at preferred temperatures of from 10 to 140°C, especially at about room temperature.

[0124] Those and other conversions can be found also in International Application WO 95/23141, published on 31.08.1995, which is incorporated herein by reference.

[0125] Salts of compounds of formula I having a salt-forming group can be prepared in a manner known *per se.* For example, acid addition salts of compounds of formula I can be obtained, for example, by treatment with an acid or a suitable anion exchange reagent.

[0126] Salts can be converted into the free compounds in customary manner, for example by treatment with a suitable basic agent.

[0127] By treatment of free compounds of formula I obtained in that manner with acid addition salts it is possible to convert salts of compounds of formula I into other salts.

[0128] Stereoisomeric mixtures, for example mixtures of diastereoisomers, cis/trans isomers or enantiomers, can be separated into the corresponding isomers in a manner known *perse* by suitable separating procedures. For example, mixtures of diastereoisomers can be separated into the individual diastereoisomers by fractional crystallisation, chromatography, solvent partition and the like. Such a separation can be carried out either at the stage of one of the starting materials or with the compounds of formula I themselves.

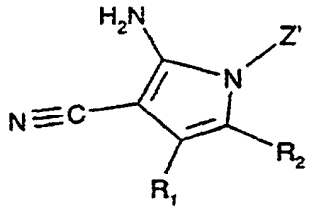
Starting materials

[0129] The starting materials of formula II are novel, are known or can be prepared according to procedures known *per se.* They can be prepared in accordance with procedures analogous to those described in German Offenlegungsschriften No. 28 18 676 (published on 8th Nov. 1979) and No. 30 36 390 (published on 13th May 1982) and European Patent Application EP 0 682 027 (published on 15th November 1995).

[0130] The starting material of formula II wherein X is chlorine is obtained, for example, from a compound analogous to formula II wherein X is hydroxy by reaction with phosphorus oxychloride (phosphoryl chloride, $P(=O)Cl_3$), with the exclusion of moisture, at reflux temperature. If desired, the further reaction of the resulting starting material of formula II wherein X is chlorine with an aza compound of formula III can be carried out in the same vessel, that is to say as a one-pot process. For that purpose the reaction mixture from the reaction with phosphorus oxychloride is concentrated

to dryness by evaporation when the reaction is complete, made into a slurry with a suitable solvent, such as n-butanol, and reacted further with the aza compound of formula III.

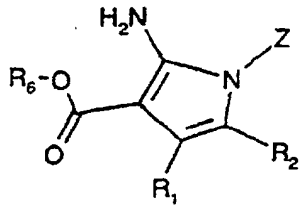
[0131] A compound analogous to formula II wherein X is hydroxy (i.e. an isomer of a compound of formula IV) is obtained, for example, from a compound of formula V



(V),

wherein Z' is 1-aryl-lower alkyl and the other symbols are as defined above, by reaction with formic acid, which is preferably used in excess with respect to the compound of formula V, for example in from 10- to 30-fold molar excess, optionally in the presence of an inert solvent, such as dimethylformamide, at elevated temperature, for example at temperatures of from 80°C to the boiling temperature.

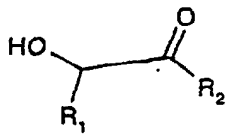
[0132] Alternatively, a compound analogous to formula II wherein X is hydroxy and the other symbols are as defined above is obtained, for example, from a compound of formula VI



(VI),

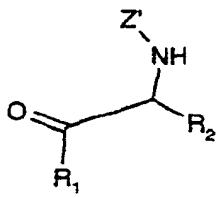
wherein R_6 is lower alkyl, such as especially ethyl, and the other symbols are as defined above, by reaction with a large excess of formamide in a mixture of anhydrous dimethylformamide and formic acid. The reaction is carried out at elevated temperature, for example from 100°C to 150°C, and preferably under a protective gas.

[0133] The 1-(Z')-2-amino-3-cyano-pyrroles of formula V used as intermediates can be prepared in good yields in accordance with published procedures known *per se* [see, for example, Roth, H.J., and Eger, K., Arch. Pharmaz. 308, 179 (1975)]. For that purpose, for example, a compound of formula VII



(VII)

is reacted first with an amine of formula Z'-NH_2 to form a compound of formula VIII

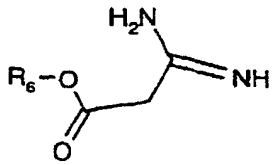


(VIII)

which is then converted with malonic acid dinitrile of the formula $CH_2(CN)_2$ into the desired intermediate of formula V.

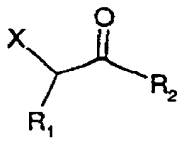
In detail, the reaction with the amine Z'-NH_2 is carried out under customary condensation conditions, for example in the presence of catalytic amounts of a strong acid, for example hydrochloric acid or p-toluenesulfonic acid, at elevated temperature (preferably boiling temperature) in a suitable solvent, for example benzene or toluene, with the separation of water, to form the respective α-aminoketone of formula VIII. The latter is not isolated but is immediately condensed with malonic acid dinitrile while hot, with the separation of water being continued, if necessary with the addition of a small amount of a base, such as piperidine, yielding a compound of formula V.

[0134] The compounds of formula VI used as intermediates wherein R_2 is N-benzyl-pyridonium-2-yl and the other symbols are as defined above are obtained, for example, by reaction of a compound of formula VI wherein R_2 is hydrogen and the other symbols are as defined above with N-benzyl-2-bromopyridonium bromide in a suitable solvent, such as a halogenated hydrocarbon, such as especially methylene chloride. The reaction is preferably carried out under a protective gas, in the dark and under anhydrous conditions at room temperature or elevated temperature, for example from 20°C to 80°C, and in the presence of 2,6-dimethylpyridine (2,6-lutidine). The other compounds of formula VI are obtained, for example, by reaction of a 2-amidino-acetic acid lower alkyl ester of formula IX



(IX),

wherein R_6 is as defined above, with a 2-X-1-R_2-ethan-1-one derivative of formula X



(X)

wherein the symbols are as defined above. The leaving group X is preferably bromine. Before the reaction begins, the 2-amidino-acetic acid lower alkyl ester of formula IX is liberated from its acid addition salt, such as especially its hydrochloride, with the aid of equimolar amounts of a base, such as especially sodium ethanolate, with ice-cooling. The reaction is carried out in a suitable solvent, especially a lower alkanol, such as preferably ethanol, at preferred temperatures of from 0°C to 50°C, especially at room temperature.

[0135] Aza compounds of formula III are known or can be prepared according to methods known *per se*; some of them are also commercially available.

[0136] For example, an aza compound of formula III can be prepared in accordance with one of the procedures described in International Application WO 95/23141, published on 31st August 1995, which is incorporated herein by reference, or in accordance with the references given therein.

[0137] For example, 2,3-dihydro-1,4-benzoxazine derivatives can be prepared according to R.C. Elderfield *et al.*, Chapter 12 in "Heterocyclic Compounds", Vol. 6, R.C. Elderfield Ed., John Wiley & Sons, Inc., New York 1957; substituted 2,3-dihydrobenzothiazinyl compounds analogously to R.C. Elderfield *et al.*, Chapter 13 of the same book; 1,2,3,4-tetrahydroquinolines and their starting materials analogously to "The Chemistry of Heterocyclic Compounds", Vol. 32, Parts 1, 2 and 3; G. Jones (Ed.), John Wiley and Sons, New York 1977; 1,2,3,4-tetrahydroquinolines substituted by lower alkyl or by unsubstituted or substituted phenyl by catalytic reduction of the corresponding quinolines using platinum oxide/hydrogen in methanol (see Honel *et al.*, *J.* Chem. Soc. Perkin I 1980, 1933-1939); substituted 2,3,4,5-tetrahydro-1H-benzo[b]azepines analogously to G.R. Proctor, Chapter II, Vol 43, "The Chemistry of Heterocyclic Compounds", Part I; A. Rosowsky (Ed.), Wiley Interscience, New York 1984; and certain 2,3,4,5-tetrahydro-1H-benzo[b] azepines and 1,2,3,4,5,6-hexahydro-1H-benzo[b]azocines by reduction from the corresponding 2,3,4,5-tetrahydro-1H-benzo[b]azepin-2-ones and 1,2,3,4,5,6-hexahydro-1H-benzo[b]azocin-2-ones (see Horning *et al.*, J. Am. Chem. Soc. 74, 5153 (1952) and Huisgen *et al.*, Liebigs Ann. Chem. 586, 30 (1954)).

[0138] Aza compounds of formula III of the indoline type can be prepared by a series of reactions known *per se*.

[0139] For example, it is possible to obtain the indoline compounds of formula III especially by reduction of corresponding indole starting compounds. For that purpose, generally the corresponding indole precursors, in which the substituents (R_3 and/or R_4) are aprotic or appropriately protected, are reacted with $ZnBH_4$ (prepared from $ZnCl_2$, see

Gensler *et al.*, J. Am. Chem. Soc. 82, 6074,6081 (1960)) in an ethereal solvent, such as diethyl ether, at a temperature of from approximately 10 to approximately 40°C, preferably at room temperature (see Korsuki *et al.*, Heterocycles 26, 1771-1774 (1987)); or the indole starting compound is reacted with a borane/pyridine complex (or another borane/tert-amine complex) in the presence or absence of a solvent, such as tetrahydrofuran, at a temperature of approximately from 10 to 30°C, preferably at room temperature, and then subjected to treatment with an acid, such as hydrochloric acid, trifluoroacetic acid or acetic acid, to form the indoline compound.

[0140] Some indoline compounds of formula III can be prepared from other indoline compounds by further modification. For example, unsubstituted or suitably substituted 5-hydroxyindolines can be prepared from the corresponding indolines by hydroxylation (see Teuber *et al.,* Chem. Ber. 89, 489-508 (1956)) and subsequent reduction of the intermediate 5-hydroxyindoles to form the 5-hydroxyindolines: potassium nitrosodisulfonate in aqueous phosphate buffer is added to the unsubstituted or appropriately substituted indoline in acetone at neutral pH and a temperature of approximately from 0 to 25°C; the resulting 5-hydroxyindole derivative is then reacted with borane/pyridine/aqueous HCl to form the 5-hydroxyindoline derivative. Unsubstituted or suitably substituted bromoindolines (for example brominated in the 4- or 6-position) can be obtained from corresponding indolines via bromination (see Miyake et al., J. Het. Chem. 20, 349-352 (1983)). That procedure can also be used for the bromination of larger ring systems (for example 1,2,3,4-tetrahydroquinolines, 2,3,4,5-tetrahydro-1H-benzo[b]azepines and 1,2,3,4,5,6-hexahydro-benzo[b]-azocines, especially in the 5/7-, 6/8- and 7/9-positions). For that purpose, generally the unsubstituted or suitably substituted indoline is reacted with bromine in the presence of a halophile, such as silver sulfate, under strongly acidic conditions and at from 0 to 25°C. In addition, certain indolines with or without 3-alkyl substituents can be prepared from the corresponding 2-(2-halophenyl)alkylamines (see German Patent Application DE 34 24 900). Furthermore, hydroxyalkylindolines can be prepared by reduction of corresponding carboxy precursors or of esters thereof (see Corey *et al.*, J. Am. Chem. Soc. 92(8), 2476-2488 (1970)). Suitably substituted lower alkyl-, lower alkenyl- or allyl-substituted indolines can be prepared from corresponding trialkylsilyl-protected 4-, 5- or 6-haloindoles by nickel-phosphine-catalysed Grignard addition (see Tamao *et al.*, Bull. Chem. Soc. Japan 49, 1958-1969 (1976)), in which case the indoline is generally N-protected by reaction with tert-butyl-dimethyl-silyl triflate in a halogenated solvent in the presence of a tertiary amine. The N-silylated haloindoline is then reacted with the corresponding alkyl-, alkenyl- or allyl-Grignard in an ethereal solvent in the presence of a suitable nickel-phosphine complex (typically bis(triphenylphosphine)nickel(II) dichloride). Subsequent treatment with methanol that contains a trace of an acid, such as trifluoroacetic acid, or with fluoride anions in a suitable solvent, such as tetrahydrofuran, frees the desired indoline derivative.

[0141] In addition, a 4-, 5-, 6- or 7-lower alkenyl-indoline or a free or tri-lower alkylsilyl-substituted lower alkynyl-indoline can be obtained by palladium-catalysed vinylation or alkynylation of a corresponding 4-, 5-, 6- or 7-haloindoline (see Kalinin, Synthesis 1992, 413-432). For the preparation of the lower alkynylindoline, the corresponding bromo- or iodo-indoline is reacted under reflux with a suitable lower alkyne or with trimethytsilylacetylene or an analogue thereof in the presence of a catalytic amount of CuI and $Pd(PPh_3)$.

[0142] 3,3-Dimethylindoline can be prepared, for example, by Lewis-acid-mediated cyclisation of N-methylallylacetanilide, followed by hydrolysis (see Synthetic Communications 25(24), 4029-4033). A suitable Lewis acid,is, for example, $AlCl_3$; the hydrolysis is carried out, for example, in the presence of hydrogen chloride.

[0143] Further preparation methods for numerous indolines, indoles, oxindoles and isatins that can be used as intermediates can be found in the literature (see "Heterocyclic Compounds with Indole and Carbazole Systems", W.C. Sumpter and F. Miller, in "The Chemistry of Heterocyclic Compounds", Vol. 8, Interscience Publishers Inc., New York 1954, and the references given therein).

[0144] The other starting compounds are known, can be prepared according to procedures known *per* se or are commercially available.

[0145] The reaction conditions used for the preparation of the starting materials are especially analogous to the reaction conditions to be found in the description and especially in the Examples.

General process conditions

[0146] All the process steps given in this text can be carried out under reaction conditions known *perse*, but preferably under those specifically mentioned, in the absence or usually in the presence of solvents or diluents, preferably those solvents or diluents that are inert towards the reagents used and are solvents therefor, in the absence or presence of catalysts, condensation agents or neutralising agents, for example ion exchangers, such as cation exchangers, for example in the H^+ form, depending upon the nature of the reaction and/or the reactants at reduced, normal or elevated temperature, for example in a temperature range of from approximately -100° to approximately 190°C, preferably from approximately - 80° to approximately 150°C, for example from -80° to -60°C, at room temperature, at from -20° to 40°C or approximately at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, optionally under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

[0147] In the case of all starting materials and intermediates, salts may be present when salt-forming groups are

present. Salts may also be present during the reaction of such compounds, provided that the reaction will not be affected.

[0148] In all reaction steps, any isomeric mixtures that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or diastereoisomeric mixtures, for example analogously to the methods described under the heading "Additional process steps".

[0149] In certain cases, for example in the case of hydrogenation, it is possible to carry out stereoselective reactions so that, for example, individual isomers may be obtained more easily.

[0150] The solvents from which those suitable for a particular reaction can be selected include, for example, water, esters, such as lower alkyl lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride, acid amides, such as dimethylformamide, bases, such as heterocyclic nitrogen bases, for example pyridine, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless the description of the processes indicates otherwise. Such solvent mixtures can also be used in working-up, for example by chromatography or partition.

[0151] The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage is used as starting material and the remaining steps are carried out or the process is interrupted at any stage or a starting material is formed under the reaction conditions or is used in the form of a reactive derivative or salt, or a compound obtainable in accordance with the process of the invention is produced under the process conditions and further processed *in situ,* it being preferable to use those starting materials which result in the compounds described above as being preferred, especially those described as being especially preferred, more especially preferred and/or very especially preferred.

[0152] The preparation of compounds of formula I (and also of intermediates) is preferably carried out analogously to the processes and process steps given in the Examples.

[0153] The compounds of formula I, including their salts, may also be obtained in the form of solvates, for example in the form of hydrates or, for example, in the form of crystals that include the solvent used for crystallisation.

Pharmaceutical compositions, the preparation thereof and the use according to the Invention of compounds of formula I and compositions comprising those compounds as active ingredient

[0154] The present invention relates also to pharmaceutical compositions that comprise one of the compounds of formula I as active ingredient and that can be used especially in the treatment of the diseases mentioned at the beginning. Special preference is given to compositions for enteral, such as nasal, buccal, rectal or especially oral, administration and parenteral, such as intravenous, intramuscular or subcutaneous, administration to warm-blooded animals, especially human beings. The compositions comprise the active ingredient on its own or preferably together with a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the disease to be treated, and on species, age, weight and individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

[0155] The invention relates also to pharmaceutical compositions for use in a method for the therapeutic treatment of the human or animal body, especially for the treatment of a tumour disease, more especially one of those mentioned above, or psoriasis, and a process for the preparation of such pharmaceutical compositions (especially as agents in tumour treatment).

[0156] Preference is given to a pharmaceutical composition suitable for administration to a warm-blooded animal, especially a human being, suffering from a disease that is responsive to the inhibition of a protein kinase, especially psoriasis or a tumour disease, comprising a compound of formula I, or a salt thereof where salt-forming groups are present, in an amount effective in the inhibition of the protein kinase, together with at least one pharmaceutically acceptable carrier.

[0157] The pharmaceutical compositions comprise from approximately 1 % to approximately 95 % active ingredient, forms of administration in single dose form preferably comprising from approximately 20 % to approximately 90 % active ingredient and forms of administration that are not in single dose form preferably comprising from approximately 5 % to approximately 20 % active ingredient. Unit dose forms are, for example, dragées, tablets, ampoules, vials, suppositories or capsules. Other forms of administration are, for example, ointments, creams, pastes, foams, tinctures, lipsticks, drops, sprays, dispersions, etc. Examples are capsules comprising from approximately 0.05 g to approximately 1.0 g of the active ingredient.

[0158] The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising procedures.

[0159] Solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions,

dispersion or suspensions, are preferably used, it being possible, for example in the case of lyophilised compositions that comprise the active ingredient alone or together with a carrier, for example mannitol, for such solutions, suspensions or dispersions to be made up prior to use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known *per se*, for example by means of conventional dissolving or lyophilising procedures. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

[0160] Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid fatty acid esters that contain as acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid, or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a mono- or poly-hydric, for example a mono-, di- or tri-hydric, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. The following examples of fatty acid esters are therefore to be mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate, Gattefossé, Paris), "Labrafil M 1944 CS" (unsaturated polyglycolised glycerides prepared by alcoholysis of apricot kernel oil and consisting of glycerides and polyethylene glycol ester; Gattefossé, France), "Labrasol" (saturated polyglycolised glycerides prepared by alcoholysis of TCM and consisting of glycerides and polyethylene glycol ester; Gattefossé, France) and/or "Miglyol 812" (triglyceride of saturated fatty acids with a chain length of C_8 to C_{12}, Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

[0161] The injection compositions are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into, for example, ampoules or vials and sealing the containers.

[0162] Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired, and if necessary by the addition of additional excipients, to form tablets or dragee cores.

[0163] Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, or alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

[0164] Dragée cores can be provided with suitable, optionally enteric, coatings, there being used *inter alia* concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the production of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

[0165] Orally administrable pharmaceutical compositions also include dry-filled capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene gylycol, to which stabilisers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

[0166] Other oral forms of administration are, for example, syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of about 5 % to 20 %, preferably about 10 %, or in a similar concentration that provides a suitable single dose, for example, when administered in measures of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packaged in single dose quantities.

[0167] Suitable rectatly administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

[0168] For parenteral administration there are suitable especially aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilisers. The active ingredient, optionally together with excipients, can also be in the form of a tyophilisate and can be made into a solution prior to parenteral administration by the addition of suitable solvents.

[0169] Solutions such as are used, for example, for parenteral administration can also be used as infusion solutions.

[0170] Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

[0171] Ointments are oil-in-water emulsions that contain up to 70 %, but preferably from 20 to 50 %, water or aqueous phase. Suitable as fatty phase are especially hydrocarbons, for example Vaseline®, paraffin oil or hard paraffins, which, for the purpose of improving the water-binding capacity, preferably contain suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, such as wool wax. Emuisfiers are corresponding lipophilic substances, such as sorbitan fatty acid esters (Spans®), for example sorbitan oleate and/or sorbitan isostearate. Additives to the aqueous phase are, for example, humectants, such as polyalcohols, for example glycerol, propylene glycol, sorbitol and/or polyethylene glycol, or preservatives and perfumes.

[0172] Fatty ointments are anhydrous and contain as base material especially hydrocarbons, for example paraffin, Vaseline® or paraffin oil, also natural or partially synthetic fats, for example coconut fatty acid triglyceride, or preferably hardened oils, for example hydrogenated groundnut or castor oil, and also fatty acid partial esters of glycerol, for example glycerol mono- and/or di-stearate, and also, for example, the fatty alcohols, emulsifiers and/or additives that increase the water-absorption mentioned in connection with the ointments.

[0173] Creams are oil-in-water emulsions that contain more than 50 % water. As oily base material there are used especially fatty alcohols, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, wool wax or beeswax, and/or hydrocarbons, for example Vaseline® (petrolatum) or paraffin oil. Suitable as emulsifiers are surface-active substances having predominantly hydrophilic properties, such as corresponding non-ionic emulsifiers, for example fatty acid esters of polyalcohols or ethyleneoxy adducts thereof, such as polyglyceric acid fatty acid esters or polyethylene sorbitan fatty acid esters (Tweens®), also polyoxyethylene fatty alcohol ethers or fatty acid esters, or corresponding ionic emulsifiers, such as alkali metal salts of fatty alcohol sulfates, for example sodium lauryl sulfate, sodium cetyl sulfate or sodium stearyl sulfate, which are customarily used in the presence of fatty alcohols, for example cetyl alcohol or stearyl alcohol. Additives to the aqueous phase are *inter alia* agents that reduce the drying out of the creams, for example polyalcohois, such as glycerol, sorbitol, propylene glycol and/or polyethylene glycois, and also preservatives and perfumes.

[0174] Pastes are creams and ointments having secretion-absorbing powder constituents, such as metal oxides, for example titanium oxide or zinc oxide, and also talc and/or aluminium silicates, the purpose of which is to bind any moisture or secretions present.

[0175] Foams are administered from pressurised containers and are liquid oil-in-water emulsions in aerosol form, there being used as propellants halogenated hydrocarbons, such as chloro-fluoro-lower alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane, or preferably non-halogenated gaseous hydrocarbons, air, N_2O or carbon dioxide. As oily phase there are used *inter alia* those used above in connection with ointments and creams, and likewise the additives mentioned therein.

[0176] Tinctures and solutions generally have an aqueous-ethanolic base to which there are added *inter alia* polyalcohols, for example glycerol, glycols and/or polyethylene glycol, as humectants to reduce evaporation, and fat-restoring substances, such as fatty acid esters with low molecular weight polyethylene glycols, i.e. lipophilic substances soluble in the aqueous mixture as a replacement for the fatty susbtances removed from the skin by the ethanol, and, if necessary, other excipients and additives.

[0177] The compounds of formula I can be administered, prophylactically or therapeutically, as such or in the form of pharmaceutical compositions, preferably in an amount effective against the said diseases, to a warm-blooded animal, for example a human being, requiring such treatment, the compounds being used especially in the form of pharmaceutical compositions. In such treatment an individual of about 70 kg body weight will be administered a daily dose of from approximately 0.1 g to approximately 5 g, preferably from approximately 0.5 g to approximately 2 g, of a compound of the present invention.

[0178] The following Examples serve to illustrate the invention but do not limit the scope thereof.

[0179] The short names and abbreviations used have the following meanings:

Abbreviations

[0180]

abs. absolute (anhydrous)

DMF	dimethylformamide
FAB-MS	Fast Atom Bombardment mass spectroscopy
m.p.	melting point
MS	mass spectroscopy
R_f	ratio of the seepage propagation in relation to the eluant in TLC
RT	room temperature
sat.	saturated
THF	tetrahydrofuran
TLC	thin-layer chromatography

Remarks:

[0181] Unless defined more specifically, "hexane" is a mixture of the hexane isomers.

Example 1: 4-(2,3-Dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine

[0182] Under an argon atmosphere, 0.2 g (1.1 mmol) of 4-chloro-5,6-dimethyl-7H-pyrrolo[2,3-d]-pyrimidine (see Liebigs Ann. Chem. 1986(9), 1485-1505; CAS-Reg. No. 82703-38-6) and 0.15 ml (1.32 mmol) of 2,3-dihydroindole (Fluka, Buchs, Switzerland) in 5 ml of abs. n-butanol are heated at reflux for 2 hours until the starting material is no longer present in TLC. The reaction mixture is concentrated by evaporation *in vacuo* at 50°C. The brown residue is dissolved in 30 ml of ethyl acetate, and 10 ml of 1N NaOH solution are added. The organic phase is separated off and washed three times with a small amount of water, dried and concentrated by evaporation. The crude product is dissolved in 10 ml of THF, and n-hexane is added until crystallisation begins. Stirring is carried out at 0°C and the product is filtered off with suction and dried under a high vacuum. Pure 4-(2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine is obtained in the form of colourless crystals having a melting point of 220-221°C. FAB-MS: $(M+H)^+ = 265$ (corresponds to $C_{16}H_{16}N_4$); R_f value (toluene-acetone - 4:6) = 0.46.

Example 2: 4-(6-Chloro-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine

[0183] This product is prepared in a manner analogous to that described in Example 1 from 4-chloro-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine and 6-chloro-2,3-dihydroindole (1.1 equivalents, see J. Org. Chem. 55(2), 580-584 (1990); GAS Reg. No. 52 537-00-5).

Example 3: 4-(6-Bromo-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine

[0184] This product is prepared in a manner analogous to that described in Example 1 from 4-chloro-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine and 6-bromo-2,3-dihydroindole (1.1 equivalents, see WO 95/23141; CAS Reg. No. 63 839-24-7).

Example 4: 4-(6-Methyl-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine

[0185] This product is prepared in a manner analogous to that described in Example 1 from 4-chloro-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine and 6-methyl-2,3-dihydroindole (1.1 equivalents, see WO 95/23141; CAS Reg. No. 86 911-82-2).

Example 5: 4-(1,2,3,4-Tetrahydroquinolin-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine

[0186] This product is prepared in a manner analogous to that described in Example 1 from 4-chloro-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine and 1,2,3,4-tetrahydroquinoline (4 equivalents, Fluka, Buchs, Switzerland). M.p: 263-264°C; FAB-MS: $(M+H)^+ = 279$ (corresponds to $C_{17}H_{18}N_4$); R_f value (toluene-acetone - (4:6)) = 0.29.

Example 6: 4-(2,3-Dihydroindol-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0187] Under a nitrogen atmosphere, 0.5 g (1.82 mmol) of 4-chloro-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine and 0.43 ml (2.1 equivalents) of 2,3-dihydroindole in 10 ml of abs. n-butanol are heated at reflux for 1.5 hours until the starting material is no longer present in TLC, the desired product precipitating out and being filtered off. The brown crude product is stirred thoroughly in about 20 ml of 1N NaOH for about 15 minutes, and the suspension is filtered with suction and the residue is washed with water, n-butanol and hexane and dried under a high vacuum. 4-(2,3-Dihydroin-

dol-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine is obtained in the form of a rust-brown powder having a melting point of > 300°C. FAB-MS: $(M+H)^+$ = 358 (corresponds to $C_{20}H_{15}N_5O_2$); R_f value (toluene-acetone - 4:6) = 0.40.

[0188] The starting material is prepared as follows:

Step 6.1: 2-Amino-3-ethoxycarbonyl-5-(4-nitro-phenyl)-pyrrole

[0189] In a dry three-necked flask, under argon, 75 ml of abs. ethanol and 6.5 g (390 mmol) of 2-amidino-acetic acid ethyl ester hydrochloride [preparation see: *Liebigs Ann. Chem.,* 1895 (1977)] are cooled to 0-5°C and 2.65 g (390 mmol) of sodium ethanolate are added. 5 g (195 mmol) of 2-bromo-1-(4-nitro-phenyl)-ethan-1-one are then added and the mixture is allowed to rise to room temperature and is stirred for a further 48 hours. The reaction mixture is then partitioned between water and ethyl acetate. The ethyl acetate phase is washed three times with water and once with sat. NaCl solution, dried and filtered, and the filtrate is concentrated by evaporation. The reddish-brown residue is made into a slurry in hexane, the title compound precipitating in the form of a crude product (purity 93 %) which is used for the next step without further purification; MS: $(M)^+$ = 275.

Step 6.2: 4-Hydroxy-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0190] 2.5 g (97 mmol) of 2-amino-3-ethoxycarbonyl-5-(4-nitro-phenyl)-pyrrole, 19.4 ml of formamide, 9.7 ml of DMF and 3.1 ml of formic acid are stirred together at 150°C for 22 hours. 1 ml of isopropanol is added to the warm reaction mixture. After the reaction mixture has cooled, the precipitated product is filtered off and washed in succession 3 times with 10 ml of ethanol each time, twice with 10 ml of isopropanol each time and twice with 10 ml of hexane each time. The title compound is obtained in the form of rust-brown crystals which are used for the next step; MS: $(M)^+$ = 256.

Step 6.3: 4-Chloro-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0191] 4-Chloro-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine is prepared, with the exclusion of moisture, by heating 4-hydroxy-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine to boiling point with an excess of $POCl_3$. The suspension is concentrated to a residual volume of 20 ml by evaporation. The residue is introduced in portions into water, neutralised with solid $NaHCO_3$, and 0.2 litre of ethyl acetate is added. Filtration and washing with hot THF yield the title compound, m.p. > 280°C; FAB-MS: $(M+H)^+$ = 275.

Example 7: 4-(2,3-Dihydroindol-1-yl)-6-(4-amino-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0192] 400 mg of 4-(2,3-dihydroindol-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine (Example 6) are hydrogenated with 150 mg of Raney nickel in methanol/THF (35:20) at RT and normal pressure for 10 hours. The catalyst is filtered off and the solution is concentrated by evaporation. The residue is dissolved in THF and the product is precipitated by the addition of hexane. 4-(2,3-Dihydroindol-1-yl)-6-(4-amino-phenyl)-7H-pyrrolo[2,3-d)pyrimidine is obtained in the form of a colourless powder. M.p. > 300°C; FAB-MS: $(M+H)^+$ = 328 (corresponds to $C_{20}H_{17}N_5$); R_f value (toluene-acetone - 4:6) = 0.21.

Example 8: 4-(6-Chloro-2,3-dihydroindol-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]-pyrimidine

[0193] This product is prepared in a manner analogous to that described in Example 6 from 4-chloro-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine and 6-chloro-2,3-dihydroindole (1.1 equivalents).

Example 9: 4-(6-Chloro-2,3-dihydroindol-1-yl)-6-(4-amino-phenyl)-7H-pyrrolo[2,3-d]-pyrimidine

[0194] This product is obtained in a manner analogous to that described in Example 7 by hydrogenation of 4-(6-chloro-2,3-dihydroindol-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine (Example 8) with Raney nickel.

Example 10: 4-(1,2,3,4-Tetrahydroquinolin-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0195] This product is prepared in a manner analogous to that described in Example 6 from 4-chloro-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine and 1,2,3,4-tetrahydroquinoline (2.1 equivalents). FAB-MS: $(M+H)^+$ = 372 (corresponds to $C_{21}H_{17}N_5O_2$); R_f value (toluene-acetone - 4:6) = 0.36.

Example 11: 4-(1,2,3,4-Tetrahydroquinolin-1-yl)-6-(4-amino-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0196] This product is obtained in a manner analogous to that described in Example 7 by hydrogenation of 4-(1,2,3,4-tetrahydroquinolin-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]-pyrimidine (Example 10) with Raney nickel. M. p. 243-245°C; FAB-MS: $(M+H)^+$ = 342 (corresponds to $C_{21}H_{19}N_5$); R_f value (toluene-acetone - 4:6) = 0.25.

Example 12: 4-(2,3-Dihydroindol-1-yl)-6-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

[0197] This product is prepared in a manner analogous to that described in Example 1 from 4-chloro-6-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine and 2,3-dihydroindole (1.1 equivalents). M.p. > 300°C; FAB-MS: $(M+H)^+$ = 343 (corresponds to $C_{21}H_{18}N_4O$).

Example 13: Dry-filled capsules

[0198] 5000 capsules, each comprising as active ingredient 0.25 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows:

Composition	
active ingredient	1250 g
talcum	180 g
wheat starch	120 g
magnesium stearate	80 g
lactose	20 g

[0199] Preparation method: The powdered substances listed above are pressed through a sieve of 0.6 mm mesh size. 0.33 g portions of the mixture are introduced into gelatin capsules using a capsule-filling machine.

Example 14: Soft capsules

[0200] 5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows:

Composition	
active ingredient	250 g
Lauroglykol	2 litres

[0201] Preparation method: The powdered active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground to a particle size of about 1 to 3 μm in a wet pulveriser. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Example 15: Soft capsules

[0202] 5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows:

Composition	
active ingredient	250 g
PEG 400	1 litre
Tween 80	1 litre

[0203] Preparation method: The powdered active ingredient is suspended in PEG 400 (polyethylene glycol of M_r from about 380 to about 420, Fluka, Switzerland) and Tween® 80 (polyoxyethylene sorbitan monolaurate, Atlas Chem. Ind., Inc., USA, supplied by Fluka, Switzerland) and ground to a particle size of about 1 to 3 μm in a wet pulveriser. 0.43 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Example 16: inhibition of the EGF-receptor-specific tyrosine kinase

[0204] In accordance with the method mentioned above and using the recombinant intracellular domain of the EGF receptor (Europ. J. Biochem. 207, 265-275 (1992)), the following IC_{50} values are obtained:

Compound of Example	IC_{50} (μM)
1	1.56
5	2.69
7	0.21
11	0.026

Example 17: Inhibition of the growth of MK (mouse keratinocyte) cells *in vitro:*

[0205] The growth of BALB/MK cells in the presence of compounds of formula I is tested in accordance with the procedure described above. The following inhibition values (IC_{50}) are obtained:

Compound of Example	IC_{50} (μM)
7	15.8
11	0.76

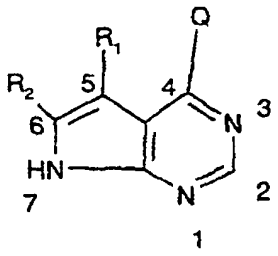
Example 18: Inhibiton of the v-abl kinase:

[0206] In accordance with the procedure mentioned above (Oncogene Research 5, 161-173 (1990) and Cancer Research 52, 4492-4498 (1992), the following IC_{50} values are obtained:

Compound of Example	IC_{50} (μM)
7	0.078
11	0.002

Claims

1. A compound of formula I



(I)

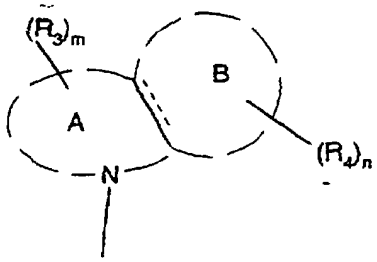
wherein

R_1 and R_2 are each independently of the other
lower alkyl; monohalo-, dihalo- or trihalo-lower alkyl; lower alkoxy; phenyl that is unsubstituted or substituted by halogen, monohalo-, dihalo- or trihalo-lower alkyl, carbamoylmethoxy, carboxy-methoxy, benzyloxycarbonyl-methoxy, lower alkoxycarbonyl-methoxy, phenyl, amino, amino-lower alkyl, lower alkanoylamino, lower alkoxycarbonylamino, phenyl-lower alkoxycarbonylamino, furoyl, thienylcarbonyl, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, lower alkoxy, lower alkanoyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, N-(N',N'-di-lower alkylaminomethylidene)-

amino, N-((N',N'-di-lower alkylamino)-(lower alkyl)-methylidene)-amino, guanidino, ureido, N^3-lower alkylureido, N^3,N^3-di-lower alkylureido, thioureido, N^3-lower alkylthioureido, N^3,N^3-di-lower alkylthioureido, lower alkanesulfonylamino, benzene- or naphthalene-sulfonylamino that is unsubstituted or lower alkyl-substituted at the benzene or naphthalene ring, azido or by nitro; hydrogen; unsubstituted or halo- or lower alkyl-substituted pyridyl; N-benzyl-pyridonium; naphthyl; cyano; carboxy; lower alkoxycarbonyl; carbamoyl; N-lower alkyl-carbamoyl; N,N-di-lower alkyl-carbamoyl; N-benzyl-carbamoyl; formyl; lower alkanoyl; lower alkenyl; lower alkenyloxy; or lower alkyl substituted by halogen, amino, lower alkylamino, piperazino, di-lower alkylamino, phenylamino or phenyl (each unsubstituted or substituted in the phenyl moiety by halogen, lower alkyl, hydroxy, lower alkanoyloxy, lower alkoxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, amino, amino-lower alkyl, lower alkanoylamino, lower alkylamino, N,N-di-lower alkylamino or by trifluoromethyl), hydroxy, lower alkoxy, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, mercapto or by a radical of the formula R_5-S(O_q)- wherein R_5 is lower alkyl and q is 0, 1 or 2, or

R_1 and R_2 together form an alkylene chain having from 2 to 5 carbon atoms which is unsubstituted or substituted by lower alkyl,

Q is heterocyclyl bonded *via* a ring nitrogen atom and having the formula IA



(IA)

wherein

m and n are each independently of the other from 0 to 3,

R_3 and R_4 are each independently of the other selected from lower alkyl; amino-lower alkyl; N-lower alkylamino-lower alkyl; N,N-di-lower alkylamino-lower alkyl; lower alkenyl; lower alkyayl, tri-lower alkylsilanyl-lower alkynyl; monohalo-, dihalo- or trihalo-lower alkyl; halogen; nitro; hydroxy; lower alkoxy; lower alkanoyloxy; isothiocyanato; phenyl that is unsubstituted or substituted by halogen, nitro, trihalo-lower alkyl, hydroxy or by lower alkyl; thienyl; phenyl-lower alkoxy that is unsubstituted or substituted in the phenyl ring by halogen, nitro, trihalo-lower alkyl, hydroxy or by lower alkyl; carboxy; lower alkoxycarbonyl; carbamoyl; N-lower alkylcarbamoyl; N,N-di-lower alkylcarbamoyl; cyano; amino; N-lower alkylamino; N,N-di-lower alkylamino; azido; benzoylamino that is unsubstituted or substituted in the benzene ring by halogen, nitro, tri-halo-lower alkyl, hydroxy or by lower alkyl; lower alkanoylamino; monohalo-, dihalo- or trihalo-lower alkylcarbonylamino; lower alkanesulfonylamino; trihalo-lower alkanesulfonylamino; lower alkylthio; lower alkylsulfinyl; lower alkanesulfonyl; pyrrol-1-yl; piperidin-1-yl; pyrrolidin-1-yl and lower alkanoyl, or two radicals R_3 together or two radicals R_4 together form lower alkylenedioxy; the ring marked A is a heterocyclyl having from 5 to 9 ring atoms and having at least one saturated bond in the ring, it being possible for a further ring hetero atom selected from O and S to be present in addition to the bonding nitrogen atom;

the ring system marked B is a free or benzo-, thieno-, furo-, pyrrolo- or dihydropyrrolo-fused carbocyclic ring having from 5 to 9 carbon atoms that is fused to the ring A and may be unsaturated, partially saturated or fully saturated;

the bond marked by a parallel dotted line between the ring systems marked A and B is either a single bond or a double bond;

and the above-mentioned prefix "lower" denotes a radical having up to and including a maximum of 7 carbon

atoms;

or a salt thereof where at least one salt-forming group is present.

2. A compound of formula I according to claim 1, wherein

R_1 and R_2 are each independently of the other
lower alkyl; monohalo-, dihalo- or trihalo-lower alkyl; lower alkoxy; phenyl that is unsubstituted or substituted by halogen, monohalo-, dihalo- or trihalo-lower alkyl, carbamoylmethoxy, carboxy-methoxy, benzyloxycarbonyl-methoxy, lower alkoxycarbonyl-methoxy, phenyl, amino, amino-lower alkyl, lower alkanoylamino, lower alkoxycarbonylamino, phenyl-lower alkoxycarbonylamino, furoyl, thienylcarbonyl, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, lower alkoxy, lower alkanoyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, N-(N',N'-di-lower alkylaminomethylidene)-amino, N-((N',N'-di-lower alkylamino)-(lower alkyl)-methylidene)-amino, guanidino, ureido, N^3-lower alkylureido, N^3,N^3-di-lower alkylureido, thioureido, N^3-lower alkylthioureido, N^3,N^3-di-lower aikylthioureido, lower alkanesulfonylamino, benzene- or naphthalene-sulfonylamino that is unsubstituted or lower alkyl-substituted at the benzene or naphthalene ring, azido or by nitro; hydrogen; unsubstituted or halo- or lower alkyl-substituted pyridyl; N-benzyl-pyridonium; naphthyl; cyano; carboxy; lower alkoxycarbonyl; carbamoyl; N-lower alkyl-carbamoyl; N,N-di-lower alkyl-carbamoyl; N-benzyl-carbamoyl; formyl; lower alkanoyl; lower alkenyl; lower alkenyloxy; or lower alkyl substituted by halogen, amino, lower alkylamino, piperazino, di-lower alkylamino, phenylamino or phenyl (each unsubstituted or substituted in the phenyl moiety by halogen, lower alkyl, hydroxy, lower alkanoyloxy, lower alkoxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, amino, amino-lower alkyl, lower alkanoylamino, lower alkylamino, N,N-di-lower alkylamino or by trifluoromethyl), hydroxy, lower alkoxy, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, mercapto or by a radical of the formula R_5-S(O_q)- wherein R_5 is lower alkyl and q is 0, 1 or 2, and

Q is a radical of formula IA selected from 2,3-dihydroindol-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl, 1,2,3,4,5,6-hexahydrobenzo[b]azocin-1-yl, 2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl, 1,2,3,5-tetrahydropyrrolo[2,3-f]indol-1-yl and 1,2,3,5,6,7-hexahydro-pyrrolo[2,3-f]indol-1-yl; each of the mentioned radicals being unsubstituted or substituted by from 1 to 3 (i.e. m + n = 0 to 3) radicals R_3 or R_4 or R_3 and R_4 selected independently of one another from lower alkyl, N,N-di-lower alkylamino-lower alkyl, lower alkynyl, tri-lower alkylsilanyl-lower alkynyl, halogen, nitro, hydroxy, lower alkoxy, isothiocyanato, unsubstituted phenyl, unsubstituted phenyl-lower alkoxy, carboxy, lower alkoxycarbonyl, amino, azido, lower alkanoylamino, trihalo-lower alkylcarbonylamino, pyrrol-1-yl and pyrrolidin-1-yl or substituted by lower alkylenedioxy that is formed by two radicals R_4 together and is bonded to two vicinal ring atoms;

or a salt thereof where at least one salt-forming group is present.

3. A compound of formula I according to claim 1, wherein

R_1 and R_2 are each independently of the other selected from hydrogen; lower alkyl; and phenyl that is unsubstituted or substituted by halogen, monohalo-, dihalo- or trihalo-lower alkyl, carbamoyl-methoxy, carboxy-methoxy, benzyloxycarbonyl-methoxy, tower alkoxycarbonyl-methoxy, phenyl, amino, amino-lower alkyl, lower alkanoylamino, lower alkoxycarbonylamino, phenyl-lower alkoxycarbonylamino, furoyl, thienylcarbonyl, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, lower alkanoyloxy, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkyl-carbamoyl, cyano, amidino, N-(N',N'-di-lower alkylaminomethylidene)-amino, N-((N',N'-di-lower alkylamino)-(lower alkyl)-methylidene)-amino, guanidino, ureido, N^3-lower alkylureido, N^3,N^3-di-lower alkylureido, thioureido, N^3-lower alkylthioureido, N^3,N^3-di-lower alkylthioureido, lower alkanesulfonylamino, benzene- or naphthalene-sulfonylamino that is unsubstituted or lower alkyl-substituted at the benzene or naphthalene ring, azido or by nitro, and
Q is a radical of formula IA selected from 2,3-dihydroindol-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl, 1,2,3,4,5,6-hexahydrobenzo[b]azocin-1-yl, 2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl, 1,2,3,5-tetrahydropyrrolo[2,3-f]indol-1-yl and 1,2,3,5,6,7-hexahydro-pyrrolo[2,3-f]indol-1-yl; each of the mentioned radicals being unsubstituted or substituted by from 1 to 3 radicals R_3 or R_4 or R_3 and R_4 selected independently of one another from lower alkyl, N,N-di-lower alkylamino-lower alkyl, lower alkynyl, tri-lower alkylsilanyl-lower alkynyl, halogen, nitro, hydroxy, lower alkoxy, isothiocyanato, unsubstituted phenyl, unsubstituted phenyl-lower alkoxy, carboxy, lower alkoxycarbonyl, amino, azido, lower alkanoylamino, trihalo-lower

alkylcarbonylamino, pyrrol-1-yl and pyrrolidin-1-yl or substituted by lower alkylenedioxy that is formed by two radicals R_4 together and is bonded to two vicinal ring atoms;

or a salt thereof.

4. A compound of formula I according to claim 1, wherein

either the two radicals R_1 and R_2 are each independently of the other lower alkyl;
or R_1 is hydrogen and R_2 is phenyl that is unsubstituted or especially substituted by amino, nitro or by methoxy; and
Q is 2,3-dihydroindol-1-yl, 6-chloro-2,3-dihydroindol-1-yl, 6-bromo-2,3-dihydroindol-1-yl, 6-methyl-2,3-dihydroindol-1 -yl or especially 1,2,3,4-tetrahydroquinolin-1-yl;

or a salt thereof.

5. A compound of formula I according to any one of the preceding claims in the form of a pharmaceutically acceptable salt.

6. 4-(2,3-Dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine according to claim 1, or a pharmaceutically acceptable salt thereof.

7. A compound of formula I according to claim 1, selected from the compounds having the names

4-(1,2,3,4-tetrahydroquinolin-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine,
4-(2,3-dihydroindol-1-yl)-6-(4-amino-phenyl)-7H-pyrrolo[2,3-d]pyrimidine,
4-(1,2,3,4-tetrahydroquinolin-1-yl)-6-(4-amino-phenyl)-7H-pyrrolo[2,3-d]pyrimidine and
4-(2,3-dihydroindol-1-yl)-6-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine,

or a pharmaceutically acceptable salt thereof.

8. A compound of formula I according to claim 1, selected from the compounds having the names

4-(6-chloro-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine,
4-(6-bromo-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine,
4-(6-methyl-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine,
4-(2,3-dihydroindol-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine,
4-(6-chloro-2,3-dihydroindol-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine,
4-(6-chloro-2,3-dihydroindol-1 -yl)-6-(4-amino-phenyl)-7H-pyrrolo[2,3-d]pyrimidine and
4-(1,2,3,4-tetrahydroquinolin-1-yl)-6-(4-nitro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine,

or a pharmaceutically acceptable salt thereof.

9. A compound of formula I according to any one of claims 1 to 8 or a pharmaceutically acceptable salt of such a compound for use in a method for the therapeutic treatment of the human or animal body.

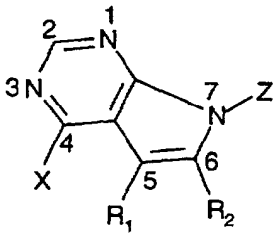
10. A pharmaceutical composition comprising a compound of formula I according to any one of claims 1 to 8 or a pharmaceutically acceptable salt of such a compound together with a pharmaceutical carrier.

11. A pharmaceutical composition for the treatment of a tumour disease in warm-blooded animals, including human beings, comprising an antitumour-effective dose of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt of such a compound together with a pharmaceutical carrier.

12. The use of a compound of formula I according to any one of claims 1 to 8 or a pharmaceutically acceptable salt of such a compound in the preparation of a pharmaceutical composition for use in the treatment of a tumour disease or psoriasis.

13. A process for the preparation of a 7H-pyrrolo[2,3-d]pyrimidine derivative of formula I
wherein

a) a pyrrolo[2,3-d]pyrimidine derivative of formula II



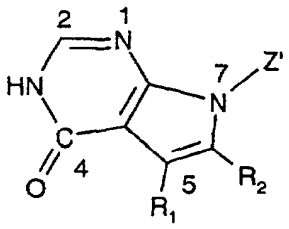
(II),

wherein X is a suitable leaving group, Z is hydrogen or 1-aryl-lower alkyl and the other substituents are as defined above for compounds of formula I, free functional groups present in the radicals R_1 and R_2 being protected if necessary by readily removable protecting groups, is reacted with an aza compound of formula III

Q-H (III),

wherein Q is as defined above for compounds of formula I, free functional groups present in the radical Q being protected if necessary by readily removable protecting groups, and any protecting groups and, if present, the 1-aryl-lower alkyl radical Z are removed, or

b) a pyrrolo[2,3-d]pyrimidin-4-one derivative of formula IV

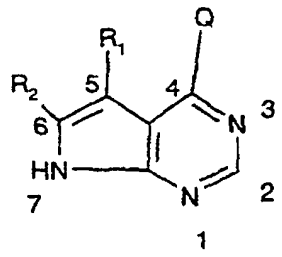


(IV),

wherein Z' is 1-aryl-lower alkyl and R_1 and R_2 are as defined above for compounds of formula I, free functional groups present in the radicals R_1 and R_2 being protected if necessary by readily removable protecting groups, is reacted in the presence of a dehydrating agent and a tertiary amine with an aza compound of the above formula III and any protecting groups present are removed;
wherein the prefix "lower" mentioned above under a) and b) denotes a radical having up to and including a maximum of 7 carbon atoms;
and, if desired, after carrying out one of the process variants a) and b), a compound of formula I is converted into a different compound of formula I; and/or, if necessary for the preparation of a salt, a resulting free compound of formula I is converted into a salt or, if necessary for the preparation of a free compound, a resulting salt of a compound of formula I is converted into the free compound; or an obtainable salt of a compound of formula I is converted into a different salt of a compound of formula I.

Patentansprüche

1. Verbindung der folgenden Formel I:



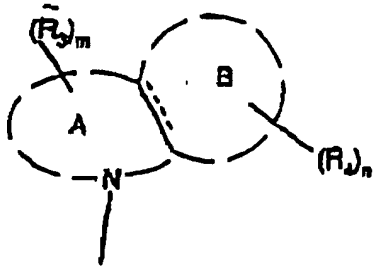
(I)

worin

R_1 und R_2 jeweils unabhängig voneinander für Niedrigalkyl; Monohalogen-, Dihalogen- oder Trihalogenniedrigalkyl; Niedrigalkoxy; Phenyl, das nicht substituiert oder durch Halogen, Monohalogen-, Diahlogen- oder Trihalogenniedrigalkyl, Carbamoylmethoxy, Carboxymethoxy, Benzyloxycarbonylmethoxy, Niedrigalkoxycarbonylmethoxy, Phenyl, Amino, Aminoniedrigalkyl, Niedrigalkanoylamino, Niedrigalkoxycarbonylamino, Phenylniedrigalkoxycarbonylamino, Furoyl, Thenylcarbonyl, N-Niedrigalkylamino, N,N-Dlniedrigalkylamino, Hydroxy, Niedrigalkoxy, Niedrigalkanoyloxy, Carboxy, Niedrigalkoxycarbonyl, Carbamoyl, N-Niedrigalkylcarbamoyl, N,N-Diniedrigalkylcarbamoyl, Cyano, Amidino, N-(N',N'-Diniedrigalkylaminomethyliden)amino, N-((N', N'-Diniedrigalkylamino)(niedrigalkyl)-methyliden)amino, Guanidino, Uredio, N^3-Niedrigalkylureido, N^3,N^3-Diniedrigalkylureido, Thioureido, N^3-Niedrigalkylthioureido, N^3,N^3-Diniedrigalkylthioureido, Niedrigalkansulfonylamino, Benzol- oder Naphthalinsulfonylamino, das nicht-substituiert oder am Benzol- oder Naphthalinring niedrigalkylsubstituiert ist, azido- oder nitrosubstituiert ist; Wasserstoff; nicht-substituiertes oder balogen- oder niedrigalkylsubstituiertes Pyridyl; N-Benzylpyridonium; Naphthyl; Cyano; Carboxy; Niedrigalkoxycarbonyl; Carbamoyl; N-Niedrigalkylcarbamoyl; N,N-Diniedrigalkylcarbamoyl; N-Benzylcarbamoyl; Formyl; Niedrigalkanoyl; Niedrigalkenyl; Niedrigalkenyloxy; oder Niedrigalkyl, das durch Halogen, Amino, Niedrigalkylamino, Piperazino, Diniedrigalkylamino, Phenylamino oder Phenyl (jeweils nicht-substituiert oder substituiert in der Phenyleinheit durch Halogen, Niedrigalkyl, Hydroxy, Niedrigalkanoyloxy, Niedrigalkoxy, Carboxy, Niedrigalkoxycarbonyl, Carbamoyl, N-Niedrigalkylcarbamoyl, N,N-Diniedrigalkylcarbamoyl, Cyano, Amidino, Amino, Aminoniedrigalkyl, Niedrigalkanoylamino, Niedrigalkylamino, N,N-Diniedrigalkylamino oder Trifluormethyl), Hydroxy, Niedrigalkoxy, Cyano, Carboxy, Niedrigalkoxycarbonyl, Carbamoyl, N-Niedrigalkylcarbamoyl, N,N-Diniedrigalkylcarbamoyl, Mercapto oder einen Rest der Formel R_5-S(O_q)-, worin R_5 für Niedrigalkyl steht und q 1 oder 2 bedeutet, substituiert ist, stehen, oder

R_1 und R_2 zusammen eine Alkylenkette mit 2 - 5 Kohlenstoffatomen bilden, die nicht-substituiert oder durch Niedrigalkyl substituiert ist,

Q für einen über ein Ringstickstoffatom gebundenen heterocyclischen Rest steht, der die folgende Formel IA besitzt:



(IA)

worin

m und n jeweils unabhängig voneinander für 0 bis 3 stehen,

R_3 und R_4 jeweils unabhängig voneinander aus Niedrigalkyl; Aminoniedrigalkyl, N-Niedrigalkylaminoniedrigalkyl; N,N-Diniedrigalkylaminoniedrigalkyl; Niedrigalkenyl; Niedrigalkinyl; Triniedrigalkylsilanylniedrigalkinyl; Monohalogen-, Dihalogen- oder Trihalogenniedrigalkyl; Halogen; Nitro; Hydroxy; Niedrigalkoxy; Niedrigalka-

noyloxy; Isothiocyanato; Phenyl, das nicht-substituiert oder durch Halogen, Nitro, Trihalogenniedrigalkyl, Hydroxy oder durch Niedrigalkyl substituiert ist; Thienyl; Phenylniedrigalkoxy, das nicht substituiert oder im Phenylring durch Halogen, Nitro, Trihalogenniedrigalkyl, Hydroxy oder durch Niedrigalkyl substituiert ist; Carboxy; Niedrigalkoxycarbonyl; Carbamoyl; N-Niedrigalkylcarbamoyl; N,N-Diniedrigalkylcarbamoyl; Cyano; Amino; N-Niedrigalkylamino; N,N-Diniedrigalkylamino; Azido; Benzoylamino, das nicht-substituiert oder im Benzolring durch Halogen, Nitro, Trihalogenniedrigalkyl, Hydroxy oder durch Niedrigalkyl substituiert ist; Niedrigalkanoylamino; Monohalogen-, Dihalogen- oder Trihalogenniedrigalkylcarbonylamino; Niedrigalkansulfonylamino; Trihalogenniedrigalkansulfonylamino; Niedrigalkylthio; Niedrigalkylsulfinyl; Niedrigalkansulfonyl; Pyrrol-1-yl; Piperidin-1-yl; Pyrrolidin-1-yl und Niedrigalkanoyl ausgewählt sind oder zwei Reste R_3 zusammen oder zwei Reste R_4 zusammen Niedrigalkylendioxy bilden;
der mit A bezeichnete Ring ein heterocyclischer Rest mit 5 bis 9 Ringatomen und mindestens einer gesättigten Bindung im Ring ist, wobei es möglich ist, dass ein weiteres Ringheteroatom, das aus O und S ausgewählt ist, neben dem bindenden Stickstoffatom vorhanden ist;
das Ringsystem mit der Bezeichnung B ein freier oder benzo-, thieno-, furo-, pyrrolo- oder dihydropyrrolokondensierter carbocyclischer Ring mit 5 bis 9 Kohlenstoffatomen ist, der an den Ring A ankondensiert ist und ungesättigt, teilweise gesättigt oder vollständig gesättigt sein kann;
die durch eine parallele gestrichelte Linie zwischen den Ringsystemen mit der Bezeichnung A und B markierte Bindung entweder eine Einfachbindung oder eine Doppelbindung ist;
und das oben genannte Präfix "Niedrig" einen Rest mit bis zu und einschließlich maximal 7 Kohlenstoffatomen bedeutet;

oder ein Salz hiervon in Fällen, in denen mindestens eine salzbildende Gruppe vorhanden ist.

2. Verbindung der Formel I nach Anspruch 1, worin R_1 und R_2 jeweils unabhängig voneinander für Niedrigalkyl; Monohalogen-, Dihalogen- oder Trihalogenniedrigalkyl; Niedrigalkoxy; Phenyl, das nicht substituiert oder durch Halogen, Monohalogen-, Diahlogen- oder Trihalogenniedrigalkyl, Carbamoylmethoxy, Carboxymethoxy, Benzyloxycarbonylmethoxy, Niedrigalkoxycarbonylmethoxy, Phenyl, Amino, Aminoniedrigalkyl, Niedrigalkanoylamino, Niedrigalkoxycarbonylamino, Phenylniedrigalkoxycarbonylamino, Furoyl, Thienylcarbonyl, N-Niedrigalkylamino, N,N-Diniedrigalkylamino, Hydroxy, Niedrigalkoxy, Niedrigalkanoyloxy, Carboxy, Niedrigalkoxycarbonyl, Carbamoyl, N-Niedrigalkylcarbamoyl, N,N-Diniedrigalkylcarbamoyl, Cyano, Amidino, N-(N',N'-Diniedrigalkylaminomethyliden)amino, N-((N',N'-Diniedrigalkylamino)(niedrigalkyl)methyliden)amino, Guanidino, Uredio, N^3-Niedrigalkylureido, N^3,N^3-Diniedrigalkylureido, Thioureido, N^3-Niedrigalkylthioureido, N^3,N^3-Diniedrigalkylthioureido, Niedrigalkansulfonylamino, Benzol- oder Naphthalinsulfonylamino, das nicht-substituiert oder am Benzol- oder Naphthalinring niedrigalkylsubstituiert ist, azido- oder nitrosubstituiert ist; Wasserstoff; nicht-substituiertes oder halogen- oder niedrigalkylsubstituiertes Pyridyl; N-Benzylpyridonium; Naphthyl; Cyano; Carboxy; Niedrigalkoxycarbonyl; Carbamoyl; N-Niedrigalkylcarbamoyl; N,N-Diniedrigalkylcarbamoyl; N-Benzylcarbamoyl; Formyl; Niedrigalkanoyl; Niedrigalkenyl; Niedrigalkenyloxy; oder Niedrigalkyl, das durch Halogen, Amino, Niedrigalkylamino, Piperazino, Diniedrigalkylamino, Phenylamino oder Phenyl (jeweils nicht-substituiert oder substituiert in der Phenyleinheit durch Halogen, Niedrigalkyl, Hydroxy, Niedrigalkanoyloxy, Niedrigalkoxy, Carboxy, Niedrigalkoxycarbonyl, Carbamoyl, N-Niedrigalkylcarbamoyl, N,N-Diniedrigalkylcarbamoyl, Cyano, Amidino, Amino, Aminoniedrigalkyl, Niedrigalkanoylamino, Niedrigalkylamino, N,N-Diniedrigalkylamino oder Trifluormethyl), Hydroxy, Niedrigalkoxy, Cyano, Carboxy, Niedrigalkoxycarbonyl, CarbamoyL N-Niedrigalkylcarbamoyl, N,N-Diniedrigalkylcarbamoyl, Mercapto oder einen Rest der Formel R_5-S(O_q)-, worin R_5 für Niedrigalkyl steht und q 0, 1 oder 2 bedeutet, substituiert ist, und
Q für einen Rest der Formel IA steht, der aus 2,3-Dihydroindol-1-yl, 1,2,3,4-Tetrahydrochinolin-1-yl, 2,3,4,5-Tetrahydro-1H-benzo[b]azepin-1-yl, 1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl, 2,3,6,7,8,9-Hexahydro-1H-benzo[g]indol-1-yl, 1,2,3,5-Tetrahydropyrrolo[2,3-f]indol-1-yl und 1,2,3,5,6,7-Hexahydropyrrolo[2,3-f]indol-1-yl ausgewählt ist, wobei jeder der genannten Reste nicht-substituiert oder durch 1 bis 3 (d.h. m + n = 0 bis 3) Reste R_3 oder R_4 oder R_3 und R_4 substituiert ist die unabhängig voneinander aus Niedrigalkyl, N,N-Diniedrigalkylaminoniedrigalkyl, Niedrigalkinyl, Triniedrigalkylsilanylniedrigalkinyl, Halogen, Nitro, Hydroxy, Niedrigalkoxy, Isothiocyanato, nicht-substituiertes Phenyl, nicht-substituiertes Phenylniedrigalkoxy, Carboxy, Niedrigalkoxycarbonyl, Amino, Azido, Niedrigalkanoylamino, Trihalogenniedrigalkylcarbonylamino, Pyrrol-1-yl und Pyrrolidin-1-yl ausgewählt sind, substituiert ist oder durch Niedrigalkylendioxy substituiert ist, das von zwei Resten R_4 zusammen gebildet wird und an zwei vicinale Ringatome gebunden ist;
oder ein Salz hiervon, in Fällen, in denen mindestens eine salzbildende Gruppe vorhanden ist

3. Verbindung der Formel I nach Anspruch 1, worin R_1 und R_2 jeweils unabhängig voneinander für Wasserstoff; Niedrigalkyl; Phenyl, das nicht substituiert oder durch Halogen, Monohalogen-, Diahlogen- oder Trihalogennied-

rigalkyl, Carbamoylmethoxy, Carboxymethoxy, Benzyloxycarbonylmethoxy, Niedrigalkoxycarbonylmethoxy, Phenyl, Amino, Aminoniedrigalkyl, Niedrigalkanoylamino, Niedrigalkoxycarbonylamino, Phenylniedrigalkoxycarbonylamino, Furoyl, Thienylcarbonyl, N-Niedrigalkylamino, N,N-Diniedrigalkylamino, Hydroxy, Niedrigalkanoyloxy, Carboxy, Niedrigalkoxycarbonyl, Carbamoyl, N-Niedrigalkylcarbamoyl, N,N-Diniedrigalkylcarbamoyl, Cyano, Amidino, N-(N',N'-Diniedrigalkylaminomethyliden)amino, N-((N',N'-Diniedrigalkylamino)(niedrigalkyl)methyliden)amino, Guanidino, Uredio, N^3-Niedrigalkylureido, N^3,N^3-Diniedrigalkylureido, Thioureido, N^3-Niedrigalkylthioureido, N^3, N^3-Diniedrigalkylthioureido, Niedrigalkansulfonylamino, Benzol- oder Naphthalinsulfonylamino, das nicht-substituiert oder am Benzol- oder Naphthalinring niedrigalkylsubstituiert ist, azido- oder nitrosubsrituiert ist, und
Q für einen Rest der Formel IA steht, der aus 2,3-Dihydroindol-1-yl, 1,2,3,4-Tetrahydrochinolin-1-yl, 2,3,4,5-Tetrahydro-1H-benzo[b]azepin-1-yl, 1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl, 2,3,6,7,8,9-Hexahydro-1H-benzo[g]indol-1-yl, 1,2,3,5-Tetrahydropyrrolo[2,3-f]indol-1-yl und 1,2,3,5,6,7-Hexahydropyrrolo[2,3-f]indol-1-yl ausgewählt ist, wobei jeder der genannten Reste nicht-substituiert oder durch 1 bis 3 Reste R_3 oder R_4 oder R_3 und R_4 substituiert ist, die unabhängig voneinander aus Niedrigalkyl, N,N-Diniedrigalkylaminoniedrigalkyl, Niedrigalkinyl, Triniedrigalkylsilanylniedrigalkinyl, Halogen, Nitro, Hydroxy, Niedrigalkoxy, Isothiocyanato, nicht-substituiertem Phenyl, nicht-substituiertem Phenylniedrigalkoxy, Carboxy, Niedrigalkoxycarbonyl, Amino, Azido, Niedrigalkanoylamino, Trihalogenniedrigalkylcarbonylamino, Pyrrol-1-yl und Pyrrolidin-1-yl ausgewählt sind, oder durch Niedrigalkylendioxy substituiert ist, das von zwei Resten R_4 zusammen gebildet wird und an zwei vicinale Ringatome gebunden ist;
oder ein Salz hiervon.

4. Verbindung der Formel I nach Anspruch 1, worin jeder der beiden Reste R_1 und R_2 unabhängig voneinander für Niedrigalkyl steht oder R_1 Wasserstoff ist und R_2 Phenyl ist, das nicht-substituiert oder insbesondere durch Amino, Nitro oder Methoxy substituiert ist und Q für 2,3-Dihydroindol-1-yl, 6-Chloro-2,3-dihydroindol-1-yl, 6-Brom-2,3-dihydroindol-1-yl, 6-Methyl-2,3-dihydroindol-1-yl oder insbesondere 1,2,3,4-Tetrahydrochinolin-1-yl steht, oder ein Salz hiervon.

5. Verbindung der Formel I nach einem der vorhergehenden Ansprüche in Form eines pharmazeutisch akzeptablen Salzes.

6. 4-(2,3-Dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrol[2,3-d]pyrimidin nach Ansprüche 1 oder ein pharmazeutisch akzeptables Salz hiervon.

7. Verbindung der Formel I nach Anspruch 1, ausgewählt aus Verbindungen mit den folgenden Bezeichnungen

4-(1,2,3,4-Tetrahydrochinolin-1-yl)-5,6-dimethyl-7H-pyrrol[2,3-d]pyrimidin,
4-(2,3-Dihydroindol-1-yl)-6-(4-aminophenyl)-7H-pyrrol[2,3-d]pyrimidin,
4-(1,2,3,4-Tetrahydrochinolin-1-yl)-6-(4-aminophenyl)-7H-pyrrol[2,3-d]pyrimidin und
4-(2,3-Dihydroindol-1-yl)-6-(4-methoxyphenyl)-7H-pyrrol[2,3-d]pyrimidin,

oder ein pharmazeutisch akzeptables Salz hiervon.

8. Verbindung der Formel I nach Anspruch 1, ausgewählt aus den Verbindungen mit den folgenden Bezeichnungen

4-(6-Chlor-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrol[2,3-d]pyrimidin.
4-(6-Brom-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrol[2,3-d]pyrimidin,
4-(6-Methyl-2,3-dihydroindol-1-yl)-5,6-dimethyl-7H-pyrrol[2,3-d]pyrimidin,
4-(2,3-Dihydroindol-1-yl)-6-(4-nitrophenyl)-7H-pyrrol[2,3-d]pyrimidin,
4-(6-Chlor-2,3-dihydroindol-1-yl)-6-(4-nitrophenyl)-7H-pyrrol[2,3-d]pyrimidin,
4-(6-Chlor-2,3-dihydroindol-1-yl)-6-(4-aminophenyl)-7H-pyrrol[2,3-d]pyrimidin und
4-(1,2,3,4-Tetrahydrochinolin-1-yl)-6-(4-nitrophenyl)-7H-pyrrol[2,3-d]pyrimidin,

oder ein pharmazeutisch akzeptables Salz hiervon.

9. Verbindung der Formel I nach einem der Ansprüche 1 bis 8 oder ein pharmazeutisch akzeptables Salz einer derartigen Verbindung zur Verwendung in einem Verfahren zur therapeutischen Behandlung des menschlichen oder tierischen Körpers.

10. Pharmazeutische Zusammensetzung, die eins Verbindung der Formel I nach einem der Ansprüche 1 bis 8 oder

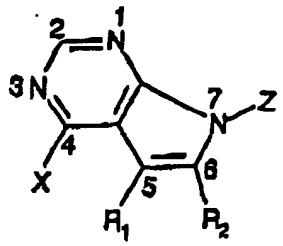
ein pharmazeutisch akzeptables Salz einer derartigen Verbindung zusammen mit einem pharmazeutischen Träger umfasst.

11. Pharmazeutische Zusammensetzung zur Behandlung einer Tumorerkrankung bei warmblütigen Tieren einschließlich Menschen, die eine antitumorwirksame Dosis einer Verbindung der Formel I nach Anspruch 1 oder eines pharmazeutisch akzeptablen Salzes einer derartigen Verbindung zusammen mit einem pharmazeutischen Träger umfasst.

12. Verwendung einer Verbindung der Formel I nach einem der Ansprüche 1 bis 8 oder eines pharmazeutisch akzeptablen Salzes einer derartigen Verbindung bei der Herstellung einer pharmazeutischen Zusammensetzung zur Verwendung bei der Behandlung einer Tumorerkrankung oder Psoriasis.

13. Verfahren zur Herstellung eines 7H-Pyrrolo[2,3-d]pyrimidinderivats der Formel I, wobei

a) ein Pyrrol[2,3-d]pyrimidinderivat der Formel II



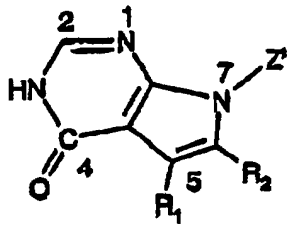
(II),

worin X für eine geeignete Abgangsgruppe steht, Z für Wasserstoff oder 1-Arylniedrigalkyl steht und die anderen Substituenten die oben für die Verbindungen der Formel I angegebenen Bedeutungen besitzen, wobei freie funktionelle Gruppen, die in den Resten R_1 und R_2 vorhanden sind, wenn nötig durch bereitwillig entfernbare Schutzgruppen geschützt sind, mit einer Azaverbindung der Formel III

Q-H (III)

umgesetzt wird, worin Q die oben für die Verbindungen der Formel I angegebene(n) Bedeutung(en) besitzt, wobei in dem Rest Q vorhandene frei funktionelle Gruppen wenn nötig durch bereitwillig entfernbare Schutzgruppen geschützt sind und beliebige Schutzgruppen und, falls vorbanden, der 1-Arylniedrigalkylrest Z entfernt werden, oder

b) ein Pyrrol[2,3-d]pyrimidin-4-on-derivat der Formel IV



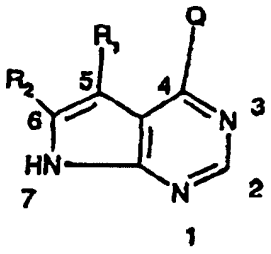
(IV),

worin Z' für 1-Arylniedrigalkyl steht und R_1 und R_2 die oben für die Verbindungen der Formel I angegebenen Bedeutungen besitzen, wobei in den Resten R_1 und R_2 vorhandene freie funktionelle Gruppen, wenn nötig durch bereitwillig entfernbare Schutzgruppen geschützt sind, in Gegenwart eines Dehydratisierungsmittels und eines tertiären Amins mit einer Azaverbindung der obigen Formel III umgesetzt wird und beliebige Schutzgruppen, die vorhanden sind, entfernt werden,
wobei das oben unter a) und b) genannte Präfix "Niedrig" einen Rest bis zu und einschließlich maximal 7 Kohlenstoffatomen bezeichnet;

und gewünschtenfalls nach Durchführen einer der Prozessvarianten a) und b) eine Verbindung der Formel I in eine unterschiedliche Verbindung der Formel I umgewandelt wind und/oder wenn nötig zur Herstellung eines Salzes eine erhaltene freie Verbindung der Formel I in ein Salz umgewandelt wird oder wenn nötig zur Herstellung einer freien Verbindung ein erhaltenes Salz einer Verbindung der Formel I in die freie Verbindung umgewandelt wird oder ein erhältliches Salz einer Verbindung der Formel I in ein unterschiedliches Salz einer Verbindung der Formel I umgewandelt wird.

Revendications

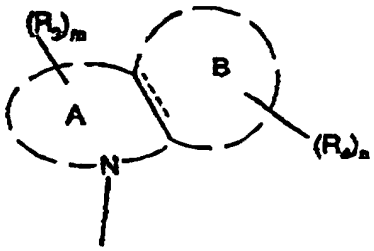
1. Composé de formule I



(I),

dans laquelle

R_1 et R_2 représentent chacun indépendamment l'un de l'autre
un alkyle inférieur ; un monohalo-, dihalo- ou trihalo-alkyle inférieur ; un alcoxy inférieur ; un phényle qui est non substitué ou substitué par un halogène, un monohalo-, dihalo- ou trihalo-alkyle inférieur, un carbamoyl-méthoxy, un carboxy-méthoxy, un benzyloxycarbonyl-méthoxy, un alcoxy inférieur-carbonyl-méthoxy, un phényle, un amino, un aminoalkyle inférieur, un alcanoyl inférieur-amino, un alcoxy inférieur-carbonylamino, un phényl-alcoxy inférieur-carbonylamino, un furoyle, un thiénylcarbonyle, un N-alkyl inférieur-amino, un N,N-di-alkyl inférieur-amino, un hydroxy, un alcoxy inférieur, un alcanoyloxy inférieur, un carboxy, un alcoxy inférieur-carbonyle, un carbamoyle, un N-alkyl inférieur-carbamoyle, un N,N-di-alkyl inférieur-carbamoyle, un cyano, un amidino, un N-(N,N'-di-alkyl inférieur-aminométhylidène)-amino, un N-(N',N'-di-alkyl inférieur-amino)-(alkyl inférieur)-méthylidène)-amino, un guanidino, un uréido, un N^3-alkyl inférieur-uréido, un N^3,N^3-di-alkyl inférieur-uréido, un thiouréido, un N^3-alkyl inférieur-thiouréido, un N^3,N^3-di-alkyl inférieur-thiouréido, un alcane inférieur-sulfonylamino, un benzène- ou un naphtalène-sulfonylamino qui est non substitué ou substitué par un alkyle inférieur sur le noyau benzène ou naphtalène, un azido ou par un nitro ; un hydrogène ; un pyridyle non substitué ou substitué par un halo ou un alkyle inférieur ; un N-benzyl-pyridonium ; un naphtyle ; un cyano ; un carboxy ; un alcoxy inférieur-carbonyle ; un carbamoyle ; un N-alkyl inférieur-carbamoyle ; un N,N-di-alkyl inférieur-carbamoyle ; un N-benzylcarbamoyle ; un formyle ; un alcanoyle inférieur ; un alcényle inférieur ; un alcényloxy inférieur ; ou un alkyle inférieur substitué par un halogène, un amino, un alkyl inférieur-amino, un pipérazino, un di-alkyl infénieur-amino, un phénylamino ou un phényle (chacun étant non substitué ou substitué dans la partie phényle par un halogène, un alkyle inférieur, un hydroxy, un aJcanoyloxy inférieur, un alcoxy inférieur, un carboxy, un alcoxy inférieur-carbonyle, un carbamoyle, un N-alkyl inférieur-carbamoyle, un N,N-di-alkyl inférieur-carbalnoyle, un cyano, un amidino, un amino, un amino-alkyle inférieur, un alcanoyl inférieur-amino, un alkyl inférieur-amino, un N,N-di-alkyl inférieur-amino ou par un trifluorométhyle), un hydroxy, un alcoxy inférieur, un cyano, un carboxy, un alcoxy inférieur-carbonyle, un carbamoyle, un N-alkyl inférieur-carbamoylc, un N,N-di-alkyl inférieur-carbamoyle, un mercapto ou par un radical de formule R_5-S(O_q)- où R_5 est un alkyle inférieur et q vaut 0, 1 ou 2, ou
R_1 et R_2 forment ensemble une chaîne alkylène ayant 2 à 5 atomes de carbone qui est non substituée ou substituée par un alkyle inférieur,
Q est un hétérocyclyle lié via un atome d'azote du cycle et répondant à la formule IA



(IA),

dans laquelle

m et n valent chacun indépendamment l'un de l'autre de 0 à 3,

R_3 et R_4 sont chacun indépendamment l'un de l'autre choisis parmi un groupe alkyle inférieur ; amino-alkyle inférieur ; N-alkyl inférieur-amino-alkyle inférieur; N,N-di-alkyl inférieur-amino-alkyle inférieur ; alcényle inférieur; alcynyle inférieur ; tri-alkyl inférieur-silanyl-alcynyle inférieur ; monohalo-, dihalo- ou trihalo-alkyle inférieur ; halogène ; nitro ; hydroxy ; alcoxy inférieur ; alcanoyloxy inférieur ; isothiocyanato ; phényle qui est non substitué ou substitué par un halogéne, un groupe nitro, trihalo-alkyle inférieur, hydroxy, ou par un alkyle inférieur ; thiényle ; phényl(alcoxy inférieur) qui est non substitué ou substitué dans le noyau phényle par un halogène, un groupe nitro, trihalo-alkyle inférieur, hydroxy, ou par un alkyle inférieur; carboxy ; alcoxy inflérieur-carbonyle ; carbamoyle ; N-alkyl inférieur-carbamoyle ; N,N-di-alkyl inférieur-carbamoyle ; cyano ; amino ; N-alkyl inférieur-amino ; N,N-di-alkyl inférieur-amino ; azido ; benzoylamino qui est non substitué ou substitué dans le noyau benzène par un halogène, un groupe nitro, trihalo-alkyle inférieur, hydroxy ou par un alkyle inférieur; alcanoyl inférieur-amino ; monohalo-, dihalo- ou trihaloalkyl inférieur-carbonylamino ; alcane inférieur-sulfonylamino ; trihaloalcane inférieur-sulfonylamino ; alkyl inférieur-thio ; alkyl inférieur-sulfinyle ; alcane inférieur-sulfonyle ; pyrrol-1-yle ; pipéridine-1-yle ; pyrrolidine-1-yle et alcanoyle inférieur, ou deux radicaux R_3 ensemble ou deux radicaux R_4 ensemble forment un alkylène inférieur-dioxy;

le noyau marqué A est un hétérocyclyle ayant 5 à 9 atomes dans le cycle et ayant au moins une liaison saturée dans le cycle, avec possibilité pour un autre hétéroatome du noyau choisi parmi O et S d'être présent outre l'atome d'azote de la liaison ;

le système cyclique marqué B est un noyau carbocyclique libre ou condensé à un groupe benzo, thiéno, furo, pyrrolo ou dihydropyrrolo ayant 5 à 9 atomes de carbone qui est condensé au noyau A et peut être insaturé, partiellement saturé ou pleinement saturé ;

la liaison marquée par une ligne pointillée parallèle entre les systèmes cycliques désignés par A et B est une liaison simple ou une liaison double ;

et le préfixe "inférieur" mentionné ci-avant dénote un radical ayant jusqu'à un maximum de 7 atomes de carbone compris ;

ou un de ses sels dans lequel au moins un groupe formant un sel est présent.

2. Composé de formule 1 selon la revendication 1, dans laquelle

R_1 et R_2 représentent chacun indépendamment l'un de l'autre

un alkyle inférieur ; un monohalo-, dihalo- ou trihalo- alkyle inférieur ; un alcoxy inférieur ; un phényle qui est non substitué ou substitué par un halogène, un monohalo-, dihalo- ou trihalo-alkyle inférieur, un carbamoyl-méthoxy, un carboxy-méthoxy, un benzyloxycarbonyl-méthoxy, un alcoxy inférieur-carbonyl-méthoxy, un phényle, un amino, un aminoalkyle inférieur, un alcanoyl inférieur-amino, un alcoxy inférieur-carbonylamino, un phényl-alcoxy inférieur-carbonylamino, un furoyle, un thiénylcarbonyle, un N-alkyl inférieur-amino, un N,N-di-allcyl inférieur-amino, un hydroxy, un alcoxy inférieur, un alcanoyloxy inférieur, un carboxy, un alcoxy inférieur-carbonyle, un carbamoyle, un N-alkyl inférieur-carbamoyle, un N,N-di-alkyl inférieur-carbamoyie, un cyano, un amidino, un N-(N',N'-di-alkyl inférieur-aminométhylidène)-amino, un N-(N,N-di-alkyl inférieur-amio)-(alkyl inférieur)-méthylidène)-amino, un guanidino, un uréido, un N^3-alkyl inférieur-uréido, un N^3,N^3-di-alkyl inférieur-uréido, un thiouréido, un N^3-alkyl inférieur-thiouréido, un N^3,N^3-di-alkyl inférieur-thiouréido, un alcane inférieur-sulfonylamino, un benzène- ou un naphtalène-sulfonylamino qui est non substitué ou substitué par un alkyle inférieur sur le noyau benzène ou naphtalène, un azido ou par un nitro ; un hydrogène ; un pyridyle non substitué ou substitué par un halo ou un alkyle inférieur ; un N-benzyl-pyridonium ; un naphtyle ; un cyano ; un carboxy ; un alcoxy inférieur-carbonyle ; un carbamoyle ; un N-alkyl inférieur-carbamoyle ; un N,N-di-alkyl

inférieur-carbamoyle ; un N-benzyl-carbamoyle ; un formyle ; un alcanoyle inférieur ; un alcényle inférieur ; un alcényloxy inférieur ; ou un alkyle inférieur substitué par un halogène, un amino, un alkyl inférieur-amino, un pipérazino, un di-alkyl inférieur-amino, un phénylamino ou un phényle (chacun étant non substitué ou substitué dans la partie phényle par un halogène, un alkyle inférieur, un hydroxy, un alcanoyloxy inférieur, un alcoxy inférieur, un carboxy, un alcoxy inférieur-carbonyle, un carbamoyle, un N-alkyl inféricur-carbamoyle, un N,N-di-alkyl inférieur-carbamoyle, un cyano, un amidino, un amino, un amino-alkyle inférieur, un alcanoyl inférieur-amino, un alkyl inférieur-amino, un N,N-di-alkyl inférieur-amino ou par un trifluorométhyle), un hydroxy, un alcoxy inférieur, un cyano, un carboxy, un alcoxy inférieur-carbonyle, un carbamoyle, un N-alkyl inférieur-carbamoyle, un N,N-di-alkyl inférieur-carbamoyle, un mercapto ou par un radical de formule R_5-S(O_q)- où R_5 est un alkyle inférieur et q vaut 0, 1 ou 2, et
Q est un radical de formule IA choisi parmi 2,3-dihydroindol-1-yle, 1,2,3,4-tétrahydroquinoléine-1-yle, 2,3,4,5-tétrahydro-1H-benzo[b]azépin-1-yle, 1,2,3,4,5,6-hexahydrobenzo[b]azocin-1-yle, 2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yle, 1,2,3,5-tétrahydropyrrolo[2,3-f]indol-1-yle et 1,2,3,5,6,7-hexahydropyrrolo [2,3-f]indol-1-yle, chacun des radicaux mentionnés étant non substitué ou substitué par 1 à 3 (c'est-à-dire que m + n = 0 à 3) radicaux R_3 ou R_4 ou R_3 et R_4 choisis indépendamment l'un de l'autre parmi un groupe alkyle inférieur, N,N-di-alkyl inférieur-amino-alkyle inférieur, alcynyle inférieur, tri-alkyl inférieur-silanyl-alcynyle inférieur, halogène, nitro, hydroxy, alcoxy inférieur, isothiocyanato, phényle non substitué, phényl non substitué-alcoxy inférieur, carboxy, alcoxy inférieur-carbonyle, amino, azido, alcanoyl inférieur-amino, trihaloalkyl inférieur-carbonyle amino, pyrrol-1-yle et pyrrolidin-1-yle ou substitués par un alkylène inférieur-dioxy qui est formé par deux radicaux R_4 ensemble et est lié par deux atomes vicinaux du cycle ;

ou un de ses sels dans lequel au moins un groupe formant un sel est présent.

3. Composé de formule I selon la revendication 1, dans lequel

R_1 et R_2 sont chacun indépendamment l'un de l'autre choisis parmi un hydrogène ;
un alkyle inférieur et un phényle qui est non substitué ou substitué par un halogène, un monohalo-, dihalo- ou trihalo-alkyls inférieur, un carbamoylméthoxy, un carboxy-méthoxy, un benzyloxycarbonyl-méthoxy, un alcoxy inférieur-carbonyl-méthoxy, un phényle, un amino, un aminoalkyle inférieur, un alcanoyl inférieur-amino, un alcoxy inférieur-carbonylamino, un phényl-alcoxy inférieur-carbonylamino, un furoyle, un thiénylcarbonyle, un N-alkyl inférieur-amino, un N,N-di-alkyl inférieur-amino, un hydroxy, un alcanoyloxy inférieur, un carboxy, un alcoxy inférieur-carbonyle, un carbamoyle, un N-alkyl inférieur-carbamoyle, un N,N-di-alkyl inférieur-carbamoyle, un cyano, un amidino, un N-(N',N'-di-alkyl inférieur-aminométhylidène)-amino, un N-(N',N'-di-alkyl inférieur-amino)-(alkyl inférieur)-méthylidène)-amino, un guanidino, un uréido, un N^3-alkyl inférieur-uréido, un N^3,N^3-di-alkyl inférieur-uréido, un thiouréido, un N^3-alkyl inférieur-thiouréido, un N^3,N^3-di-alkyl inférieur-thiouréido, un alcane inférieur-sulfonylamino, un benzène- ou un naphtalène-sulfonylamino qui est non substitué ou substitué par un alkyle inférieur sur le noyau benzène ou naphtalène, un azido ou par un nitro, et
Q est un radical de formule IA choisi parmi 2,3-dihydroindol-1-yle, 1,2,3,4-tétrahydroquinoléine-1-yle, 2,3,4,5-tétrahydro-1H-bonzo[b]azépin-1-yle, 1,2,3,4,5,6-hexahydrobenzo[b]azocin-1-yle, 2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yle, 1,2,3,5-tétrahydropyrrolo[2,3-f]indol-1-yle et 1,2,3,5,6,7-hexahydropyrrolo [2,3-f]indol-1-yle, chacun des radicaux mentionnés étant non substitué ou substitué par 1 à 3 radicaux R_3 ou R_4 ou R_3 et R_4 choisis indépendamment l'un de l'autre parmi un groupe alkyle inférieur, N,N-di-alkyl inférieur-amino-alkyle inférieur, alcynyle inférieur, tri-alkyl inférieur-silanyl-alcynyle inférieur, halogène, nitro, hydroxy, alcoxy inférieur, isothiocyanato, phényle non substitué, phényl non substitué-alcoxy inférieur, carboxy, alcoxy inférieur-carbonyle, amino, azido, alcanoyl inférieur-amino, trihalo-alkyle inférieur-carbonylamino, pyrrol-1-yle et pyrrolidin-1-yle ou substitués par un alkylène inférieur-dioxy qui est formé par deux radicaux R_4 ensemble et est lié par deux atomes vicinaux du cycle ;

ou un de ses sels.

4. Composé de formule I selon la revendication 1, dans lequel,
ou bien les deux radicaux R_1 et R_2 représentent chacun indépendamment l'un de l'autre un alkyle inférieur ;
ou bien R_1 est un hydrogène et R_2 est un phényle qui est non substitué ou substitué en particulier par un amino, un nitro ou par un méthoxy ; et
Q est un 2,3-dihydroindol-1-yle, 6-chloro-2,3-dihydroindol-1-yle, 6-bromo-2,3-dihydroindol-1-yle, 6-méthyl-2,3-dihydroindol-1-yle ou en particulier un 1,2,3,4-tétrahydroquinoléin-1-yle ;
ou un de ses sels.

5. Composé de formule I selon l'une quelconque des revendications précédentes sous la forme d'un sel pharmaceutiquement acceptable.

6. 4-(2,3-dihydroindol-1-yl)-5,6-diméthyl-7H-pyrrolo[2,3-d]pyrimidine selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables.

7. Composé de formule I selon la revendication 1, choisi parmi les composés suivants

4-(1,2,3,4-tétrahydroquinoléin-1-yl)-5,6-diméthyl-7H-pyrrolo[2,3-d]pyrimidine,
4-(2,3-dihydroindol-1-yl)-6-(4-amino-phényl)-7H-pyrrolo[2,3-d]pyrimidine,
4-(1,2,3,4-tétrahydroquinoléin-1-yl)-6-(4-amino-phényl)-7H-pyrrolo[2,3-d]pyrimidine, et
4-(2,3-dihydroindol-1-yl)-6-(4-méthoxy-phényl)-7H-pyrrolo[2,3-d]pyrimidine

ou un de leurs sels phannaceutiquement acceptables.

8. Composé de formule I selon la revendication 1, choisi parmi les composés suivants :

4-(6-chloro-2,3-dihydroindol-1-yl)-5,6-diméthyl-7H-pyrrolo[2,3-d]pyrimidine,
4-(6-bromo-2,3-dihydroindol-1-yl)-5,6-diméthyl-7H-pyrrolo[2,3-d]pyrimidine,
4-(6-méthyl-2,3-dihydroindol-1-yl)-5,6-diméthyl-7H-pyrrolo[2,3-d]pyrimidine,
4-(2,3-dihydroindol-1-yl)-6-(4-mitrophényl)-7H-pyrrolo[2,3-d]pyrimidine,
4-(6-chloro-2,3-dihydroindol-1-yl)-6-(4-nitrophényl)-7H-pyrrolo[2,3-d]pyrimidine,
4-(6-chloro-2,3-dihydroindol-1-yl)-6-(4-amino-phényl)-7H-pyrrolo[2,3-d]pyrimidine, et
4-(1,2,3,4-tétrahydroquinoléin-1-yl)-6-(4-nitro-phényl)-7H-pyrrolo[2,3-d]pyrimidine, ou un de leurs sels pharmaceutiquement acceptables.

9. Composé de formule I selon l'une quelconque des revendications 1 à 8 ou un sel pharmaceutiquement acceptable d'un tel composé pour utilisation dans un procédé de traitement thérapeutique humain ou animal.

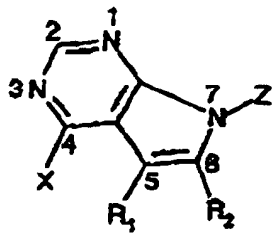
10. Composition pharmaceutique comprenant un composé de formule I selon l'une quelconque des revendications 1 à 8 ou un sel pharmaceutiquement acceptable d'un tel composé associé à un véhicule pharmaceutique.

11. Composition pharmaceutique pour le traitement des maladies tumorales chez les homéothermes, y compris les êtres humains, comprenant une quantité antitumorale efficace d'un composé de formule 1 selon la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé avec un véhicule pharmaceutique.

12. Utilisation d'un composé de formule I selon l'une quelconque des revendications 1 à 8 ou d'un sel pharmaceutiquement acceptable d'un tel composé dans la préparation d'une composition pharmaceutique pour utilisation dans le traitement des maladies tumorales ou du psoriasis.

13. Procédé pour la préparation d'un dérivé de 7H-pyrrolo[2,3-d]pyrimidine de formule I dans lequel

a) on fait réagir un dérivé pyrrolo[2,3-d]pyrimidine de formule II



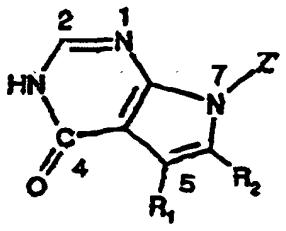
(II),

dans laquelle X est un groupe partant convenable, Z représente un hydrogène ou un 1-aryl-alkyle inférieur et les autres substituants sont tels que définis ci-avant pour les composés de formule I, les groupes fonctionnels libres présents dans les radicaux R_1 et R_2 étant protégés si nécessaire par des groupes protecteurs faciles à

éliminer,
avec un composé aza de formule III,

Q-H (III),

dans laquelle Q est tel que défini ci-avant pour les composés de formule I, les groupes fonctionnels libres présents dans le radical Q étant protégés si nécessaire par des groupes protecteurs faciles à enlever, et on éliminc les groupes protecteurs éventuels, et s'il est présent, le radical Z 1-aryl-alkyle inférieur ou
b) on fait réagir un dérivé pyrrolo[2,3-d]pyrimidin-4-one de formule IV



(IV),

dans laquelle Z' est un 1-aryl-alkyle inférieur et R_1 et R_2 sont tels que définis ci-avant pour les composés de formule I, les groupes fonctionnels libres présents dans les radicaux R_1 et R_2 étant protégés si nécessaire par des groupes protecteurs faciles à éliminer,
en présence d'un agent déshydratant et d'une amine tertiaire, avec un composé aza de formule III ci-dessus et on retire les groupes protecteurs éventuellement présents ;
le préfixe "inférieur" mentionné ci-avant en a) et b) désignant un radical ayant jusqu'à 7 atomes de carbone inclus au maximum ;
et, si on le désire, après avoir réalisé l'une des variantes a) et b) du procédé, on transforme un composé de formule I en un composé différent de formule I ; et/ou, si nécessaire pour la préparation d'un sel, on transforme un composé libre de formule I résultant en un sel ou, si nécessaire pour la préparation d'un composé libre, on transforme un sel résultant d'un composé de formule I en le composé libre ; ou on transforme un sel que l'on peut obtenir d'un composé de formule I en un sel différent d'un composé de formule I.